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(54) **NOVEL QUINOLONE DERIVATIVE OR SALT THEREOF AND ANTIBACTERIAL CONTAINING THE SAME.**

(57) A quinolone derivative represented by general formula (1) or a salt thereof, and an antibacterial containing the same as the active ingredient, wherein R^1 represents hydrogen or a protective group; R^2 represents hydrogen, halogen or lower alkyl; X represents hydrogen or halogen; Y represents halogen, optionally substituted cyclic amino, optionally substituted lower cycloalkenyl, or R^3-$(CH_2)_m$-A- wherein R^3 represents hydrogen or optionally substituted amino, A represents oxygen or sulfur, and m represents a number of 0 to 3; Z represents

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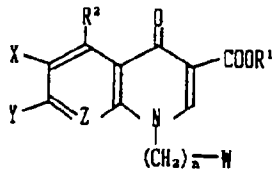
nitrogen or C-R^4 wherein R^4 represents hydrogen or halogen; W represents an optionally substituted five-membered heterocyclic group having three or more heteroatoms among which at least two are nitrogen; and n represents a number of 0 to 2. This compound has a potent antibacterial activity and a high safety, thus being useful as human and animal drugs, medicines for fish, agricultural chemicals, and food preservatives.



(1)

Technical Field

The present invention relates to novel quinolone derivatives and salts thereof having excellent antibacterial activity and oral-route absorption, and antibacterial agents containing the compounds.

Background Art

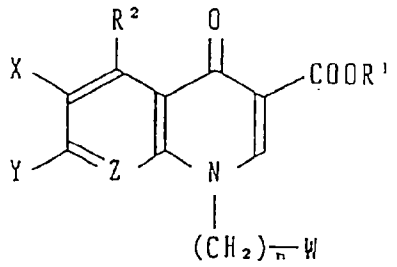
Among the compounds which have pyridonecarboxylic acid as a basic skeleton, many are known to be useful as synthetic antibacterial agents due to their excellent antibacterial activities and a broad antibacterial spectrum. Mention may be given to norfloxacin (Japanese Patent Application Kokai No. 141286/1978), enoxacin (Japanese Patent Application Kokai No. 31042/1980), ofloxacin (Japanese Patent Application Kokai No. 46986/1982), cyprofloxacin (Japanese Patent Application Kokai No. 76667/1983) and the like, which have widely found a clinical utility as therapeutic agents for infectious diseases.

These compounds, however, are not sufficiently satisfactory in terms of antibacterial activities, intestinal tract absorption, metabolic stability, minimized adverse side effects, and the like, and hence novel compounds which meet these requirements have been desired.

Under the above circumstances, the present inventors have conducted careful studies with a view toward obtaining clinically excellent synthetic antibacterial agents, and have found that the compounds represented by formula (1) described hereinafter provide excellent oral absorption, exhibit excellent antibacterial activities against gram negative and gram positive bacteria and thus are very useful as synthetic antibacterial agents, leading to the completion of the invention.

Disclosure of the Invention

The present invention is to provide quinolone derivatives represented by the below-described formula (1), salts thereof and antibacterial agents containing the derivatives or salts:



(1)

wherein R^1 represents a hydrogen atom, halogen atom or a carboxyl protective group, R^2 represents a hydrogen atom, halogen atom or a lower alkyl group, X represents a hydrogen atom or a halogen atom, Y represents a halogen atom, a cyclic amino group which may have a substituent, a cyclo- lower alkenyl group which may have a substituent, or a group R^3-$(CH_2)_m$-A- (wherein R^3 represents a hydrogen atom or an amino group which may have a substituent, A represents an oxygen atom or a sulfur atom and m represents a number of 0 to 3), Z represents a nitrogen atom or a group C-R^4 (wherein R^4 represents a hydrogen atom or a halogen atom), W represents a five-membered heterocyclic group which may have a substituent and which has 3 or more hetero-atoms, among which at least 2 hetero-atoms are nitrogen atoms, and n represents a number of 0 to 2.

Since the present compounds (1) exhibit excellent antibacterial activities and are highly safe, they are useful as pharmaceuticals for the human and animals, medicines for fishes, pesticides, preservatives for foods, and the like.

Best Mode for Carrying out the invention

In the present invention, the term "lower" used in the expressions of the substituents of the quinolone derivatives or their salts (1) means that the group referred to has 1-7, preferably 1-5 carbon atoms when the substituents are linear or branched, and has 3-7 carbon atoms when the substituents are cyclic.

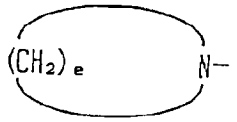
The carboxy protective group represented by R^1 is the ester residue of a carboxylic acid ester, and encompasses any groups which are relatively easily cleaved and produce corresponding free carboxyl groups. Examples of the carboxy protective group include those removable upon treatment under mild conditions such as hydrolysis or catalytic reduction, such as lower alkyl groups (e.g., methyl, ethyl, n-propyl, t-butyl, etc.), lower alkenyl groups (e.g., allyl, etc.), aralkyl groups (e.g., benzyl, etc.) or aryl groups (e.g., phenyl, etc.); and those readily removable in a living body, such as lower alkanoyloxy-lower alkyl groups (e.g., acetoxymethyl, pivaloyloxymethyl, etc.), lower alkoxycarbonyloxy-lower alkyl groups (e.g., methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl, etc.), lower alkoxymethyl groups (e.g. methoxymethyl, etc.), lactonyl groups (e.g., phthalidyl, etc.), di(lower alkyl)amino-lower alkyl groups (e.g., 1-dimethylaminoethyl, etc.), (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group, and the like.

Examples of lower alkyl groups represented by R^2 include methyl group, ethyl group, n-propyl group and t-butyl group.

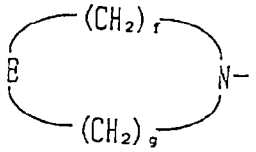
Examples of halogen atoms represented by X and R^2 include a fluorine atom, chlorine atom, bromine atom, with a fluorine atom being preferred.

Halogen atoms represented by Y are the same as those represented by X, among which a fluorine atom and a chlorine atom are preferred.

Cyclic amino groups, represented by Y, which may have a substituent are saturated or unsaturated, and they may contain further one or more hetero-atoms such as nitrogen, oxygen, sulfur, etc., or a carbonyl carbon in the ring thereof. They may be mono, di, or tri-cyclic. Examples of such cyclic amino groups include: saturated or unsaturated monocyclic 3 to 7 membered cyclic amino groups having one nitrogen atom, such as azirydin-1-yl, azetidin-1-yl, pyrrolidin-1-yl, pyrrolin-1-yl, pyrrol-1-yl, dihydropyridin-1-yl, piperidino, dihydroazepin-1-yl, perhydroazepin-1-yl; saturated or unsaturated monocyclic 3 to 7 membered cyclic amino groups having two nitrogen atoms, such as imidazol-1-yl, imidazolidin-1-yl, imidazolin-1-yl, pyrazolidin-1-yl, piperazin-1-yl, 1, 4-dihydropyridin-1-yl, 1,2-dihydropyrimidin-1-yl, perhydropyrazin-1-yl and homopiperazin-1-yl; saturated or unsaturated monocyclic 3 to 7 membered cyclic amino groups having three or more nitrogen atoms, such as 1,2,4-triazole-1-yl, 1,2,3-triazole-1-yl, 1,2-dihydro-1,2,4-triazin-1-yl and perhydro-S-triazin-1-yl; saturated or unsaturated monocyclic 3 to 7 membered cyclic amino group which has a hetero-atom selected from the group consisting of nitrogen, oxygen and sulfur, as well as a nitrogen atom, such as oxazolidin-3-yl, isoxazolidin-2-yl, morpholino, 1,3-oxazin-3-yl, tiazolidin-1-yl, isotiazolidin-1-yl, thiomorpholin-1-yl, homothiomorpholin-1-yl, 1,2,4-thiadiazolin-2-yl, 1,2,3-thiadiazolidin-2-yl; saturated or unsaturated monocyclic cyclic amino groups of di or tri-cyclic, such as isoindolin-2-yl, indolin-1-yl, 1H-indazol-1-yl, purin-7-yl and tetrahydroquinolin-1-yl; and spiro or bridge type, saturated or unsaturated 5 to 12 membered cyclic amino groups, such as 2,8-diazaspiro[4,4]nonan-2-yl, 7-azabicyclo-[2.2.1]-heptan-7-yl, 2,8-diazabicyclo-[4,3,0]nonane, 5-methyl-2,5-diazabicyclo[2.2.1]heptane and 2,5-diazabicyclo-[2.2.1]heptane. Preferred examples of such cyclic amino groups are those represented by the following formulas (a)-(t).



(a)



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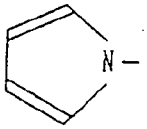

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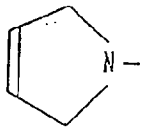

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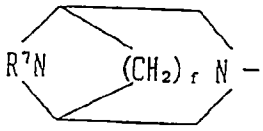

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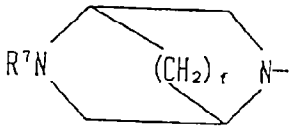

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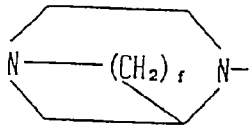

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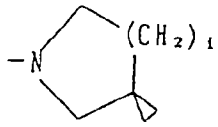

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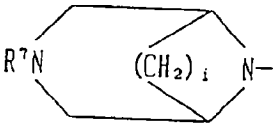
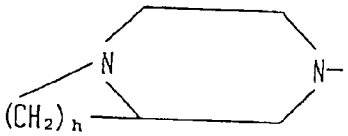


(i)



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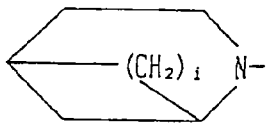

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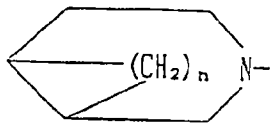

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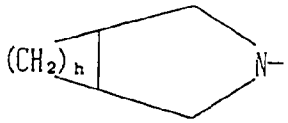

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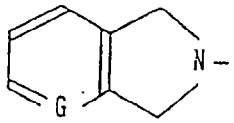

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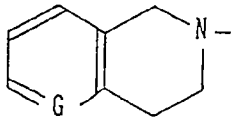

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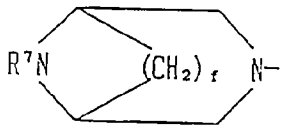

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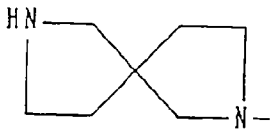

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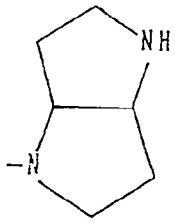

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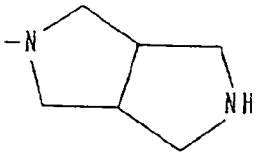

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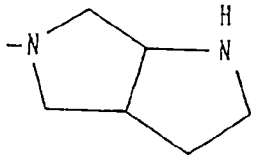


(t)

In the above formulas, E is an oxygen atom, a sulfur atom, -NR^7 or -CONR^7 (R^7 is a hydrogen atom, a hydroxyl group, a lower alkyl group, a cyclo- lower alkyl group, an aralkyl group, an alkenyl group, and acyl group or a hydroxy- lower alkyl group), G is CH or N, e is a number of 3-5, f is a number of 1-3, g is a number of 0-2 and h is 3 or 4, i is 1 or 2.

Cyclic atoms of these cyclic amino groups may be substituted with suitable substituents. Preferable examples of such substituents include lower alkyl groups, lower alkenyl groups, lower aralkyl groups, aryl groups, hydroxyl groups, hydroxy- lower alkyl groups, substituted or unsubstituted amino groups, substituted or unsubstituted amino- lower alkyl groups, cyclic amino groups as mentioned above, alkoxy groups, alkoxy- lower alkyl groups, halogen atoms, halo- lower alkyl groups, acyloxy groups, acyloxy- lower alkyl groups, acyl groups, carboxyl groups, carboxy- lower alkyl groups, alkoxycarbonyl- lower alkyl groups,

mercapto groups, lower alkylthio groups, cyano groups and nitro groups.

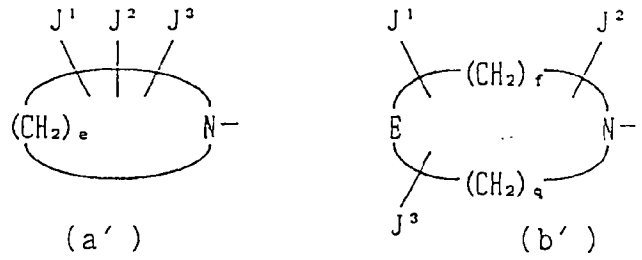
Examples of the lower alkyl groups include methyl group and ethyl group, n-propyl group and the like. Examples of the lower alkenyl groups include vinyl group and allyl group and the like. Examples of the lower aralkyl groups include benzyl group and 1-phenylethyl group and the like. Examples of the aryl groups include phenyl group and the like. Examples of the hydroxy- lower alkyl groups include hydroxymethyl group, hydroxyethyl group, hydroxypropyl group and the like. Examples of the amino- lower alkyl groups include aminomethyl group, 1-aminoethyl group, 2-aminoethyl group, 1-amino-1-methylethyl group and the like. Examples of the alkoxy groups include methoxy group, ethyoxy group, n-propoxy group and the like. Examples of the alkoxy- lower alkyl groups include methoxymethyl group, ethoxymethyl group and the like. Examples of the halogen atoms include fluorine atom, chlorine atom, bromine atom and the like. Examples of the halo- lower alkyl groups include fluoromethyl group, trifluoromethyl group and the like. Examples of the acyloxy groups include acetoxy group, benzoyloxy group and the like. Examples of the acyloxy- lower alkyl groups include acetoxymethyl group benzoyloxymethyl group and the like. Examples of the acyl groups include lower alkanoyl group such as formyl, acetyl and the like, lower alkoxycarbonyl group such as methoxycarbonyl and ethoxycarbonyl, and aromatic acyl group such as benzoyl, phenoxycarbonyl, and the like. Examples of the carboxy- lower alkyl groups include carboxymethyl group, carboxyethyl group and the like. Examples of the alkoxycarbonyl- lower alkyl groups include methoxycarbonylmethyl group, t-butoxycarbonylmethyl group and the like. Examples of the lower alkylthio groups include methylthio group, ethylthio group and the like.

As the substituent of the substituted amino group and the substituted amino- lower alkyl group, there can be mentioned lower alkyl groups (e.g., methyl group, ethyl group, etc.), lower cycloalkyl groups (e.g., cyclopropyl group, cyclobutyl group, cyclopentyl group, etc.), lower alkenyl groups (e.g., vinyl group, ally group, etc.), lower aralkyl groups (e.g., benzyl group, 1-phenylethyl group, etc.), aryl groups (e.g., phenyl group, etc.), acyl groups (e.g., lower alkanoyl groups such as formyl and acetyl, lower alkoxycarbonyl groups such as methoxycarbonyl and ethoxycarbonyl, etc.), amino acid residues or peptide residues (e.g., glycyl-, leucyl-, valyl, alanyl-, phenylalanyl-, alanyl-alanyl, glycyl-valyl and glycyl-glycyl-valyl- groups, etc.), amino acid residues or peptide residues such as the above-described groups protected by a protection group such as acyl group, lower aralkyl group or the like commonly used in the peptide chemistry; and cyclic amino groups. The same or different kinds of 1 to 2 substituents can be freely selected. Compounds protected by the above-mentioned amino acid residues or peptide residues expectedly have an improved water-solubility.

Preferable examples of the substituted amino group and the substituted amino- lower alkyl group include methylamino group, ethylamino group, dimethylamino group, methylaminomethyl group, ethylaminomethyl group, dimethylaminomethyl group, glycyl-amino group, leucyl-amino group, valyl-amino group, alanyl-amino group, alanyl-alanyl-amino group and the like.

Regarding the groups represented by R^7, there are given methyl group, ethyl group or the like for the lower alkyl group; cyclopropyl group, cyclobutyl group or the like for the cyclo- lower alkyl group; benzyl group, 1-phenylethyl group or the like for the aralkyl group; vinyl group, allyl group or the like for the alkenyl group; formyl group, acetyl group, methoxycarbonyl group, ethoxycarbonyl group or the like for the acyl group; and hydroxymethyl group, hydroxyethyl group or the like for the hydroxy- lower alkyl group.

Among the cyclic amino groups represented by the formulas (a) and (b), those represented by the following formulas (a') and (b') are particularly preferred.



(a') (b')

wherein E, e, f and g have the same meaning as defined for the formulas (a) and (b), J^1, J^2 and J^3 may be the same or different and are one of a hydrogen atom, a lower alkyl group, a lower alkenyl group, a lower aralkyl group, an aryl group, a hydroxyl group, a hydroxy- lower alkyl group, a amino group which may have a substituent, a amino- lower alkyl group which may have a substituent, a pyrrolidinyl group, a

piperidino group, an azetidinyl group, an alkoxy group, an alkoxy- lower alkyl group, a halogen atom, a halo-lower alkyl group, an acyloxy group, an acyloxy- lower alkyl group, an acyl group, a carboxyl group, a carboxy- lower alkyl group, an alkoxycarbonyl- lower alkyl group, a mercapto group, a lower alkylthio group, a cyano group and nitoro group.

The definitions of substituents of the J^1, J^2 and J^3 and their preferable examples are the same as those described in relation to the substituents for the above-mentioned cyclic amino groups.

Examples of the heterocyclic ring groups represented by formula (a') include azetidinyl group, pyrrolidinyl group and piperidino group. Examples of the heterocyclic ring groups represented by formula (b') include piperazinyl group, morpholino group, thiomorpholino group, homopiperazinyl group, thiazolidinyl group, oxazolidinyl group and 3-oxo-1-piperazinyl group.

Particularly, preferable examples of groups represented by formulas (a') and (b') are as follows:

3-hydroxyazetidinyl group, 3-aminoazetidinyl group, 3-(N-t-butoxycarbonylamino)azetidinyl group, 3-acetylamino-azetidinyl group, 3-methylaminoazetidinyl group, 3-dimethyl-aminoazetidinyl group, 3-methylazetidinyl group, 3-amino-2-methylazetidinyl group; pyrrolidinyl group, 3-hydroxy- pyrrolidinyl group, 3,4-dihydroxypyrrolidinyl group, 3-methoxypyrrolidinyl group, 3-methylpyrrolidinyl group, 3-hydroxy-4-methyl-pyrrolidinyl group, 3-aminopyrrolidinyl group, 3-methylaminopyrrolidinyl group, 3-dimethylamino pyrrolidinyl group, 3-ethylaminopyrrolidinyl group, 3-diethylaminopyrrolidinyl group, 3-acetylaminopyrrolidinyl group, 3-t-butoxycarbonylaminopyrrolidinyl group, 3-(N-acetyl)methylaminopyrrolidinyl group, 3-(t-butoxycarbonyl)methylaminopyrrolidinyl group, 3-aminomethylpyrrolidinyl group, 3-methylaminomethylpyrrolidinyl group, 3-dimethylaminomethylpyrrolidinyl group; 3-ethylaminomethylpyrrolidinyl group, 3-diethylaminomethylpyrrolidinyl group, 3-(N-acetyl)aminomethylpyrrolidinyl group, 3-(t-butoxycarbonyl)-aminomethylpyrrolidinyl group, 3-(N-acetyl)methylaminomethylpyrrolidinyl group, 3-(t-butoxycarbonyl)-methylaminomethylpyrrolidinyl group, 3-(1-aminoethyl)pyrrolidinyl group, 3-(2-aminoethyl)pyrrolidinyl group, 3-(1-amino-1-methylethyl)pyrrolidinyl group, 3-(1-methylaminoethyl)pyrrolidinyl group, 3-(1-dimethylaminoethyl)pyrrolidinyl group; 3-amino-3-methylpyrrolidinyl group, 3-amino-4-methylpyrrolidinyl group, 3-amino-5-methylpyrrolidinyl group, 3-methylamino-4-methylpyrrolidinyl group, 3-dimethylamino-4-methylpyrrolidinyl group, 3-ethyl-amino-4-methylpyrrolidinyl group, 3-diethylamino-3-methyl-pyrrolidinyl group, 3-diethylamino-4-methylpyrrolidinyl group, 3-aminomethyl-4-methylpyrrolidinyl group, 3-methyl-aminomethyl-4-methylpyrrolidinyl group; 3-dimethylaminomethyl-4-methylpyrrolidinyl group, 3-ethyl-aminomethyl-4-methylpyrrolidinyl group, 3-(1-aminoethyl)-4-methylpyrrolidinyl group, 3-(2-aminoethyl)-4-methylpyrrolidinyl group, 3-amino-4-ethylpyrrolidinyl group, 3-methylamino-4-ethylpyrrolidinyl group, 3-dimethylamino-4-ethylpyrrolidinyl group, 3-ethylamino-4-ethylpyrrolidinyl group, 3-diethylamino-4-ethylpyrrolidinyl group, 3-aminomethyl-4-ethylpyrrolidinyl group, 3-methylaminomethyl-4-ethylpyrrolidinyl group; 3-dimethylaminomethyl-4-ethylpyrrolidinyl group; 3-amino-3-methylpyrrolidinyl group, 3-methylamino-3-methylpyrrolidinyl group, 3-dimethylamino-3-methylpyrrolidinyl group, 3-amino-3,4-dimethylpyrrolidinyl group, 3-amino-4,4-dimethylpyrrolidinyl group, 3-amino-4,5-dimethylpyrrolidinyl group, 3-amino-2,4-dimethylpyrrolidinyl group, 3-methylamino-3,4-dimethylpyrrolidinyl group; 2-methyl-3-aminopyrrolidinyl group, 2-methyl-3-dimethylaminopyrrolidinyl group, 3-amino-4-vinylpyrrolidinyl group, 3-amino-4-methoxypyrrolidinyl group, 3-amino-4-methoxymethylpyrrolidinyl group, 3-methylamino-4-methoxypyrrolidinyl group, 3-dimethylamino-4-methoxypyrrolidinyl group, 3-ethylamino-4-methoxypyrrolidinyl group, 3-dimethylamino-4-methoxypyrrolidinyl group; 3-benzylamino-4-methoxypyrrolidinyl group, 3-aminomethyl-4-methoxypyrrolidinyl group, 3-methylaminomethyl-4-methoxypyrrolidinyl group, 3-dimethylaminomethyl-4-methoxypyrrolidinyl group, 3-ethylaminomethyl-4-methoxypyrrolidinyl group, 3-aminomethyl-3-methoxypyrrolidinyl group, 3-methylaminomethyl-3-methoxypyrrolodinyl group, 3-dimethylaminomethyl-3-methoxypyrrolidinyl group, 3-amino-4-ethoxypyrrolidinyl group, 3-methylamino-4-ethoxypyrrolidinyl group, 3-dimethylamino-4-ethoxypyrrolidinyl group, 3-methylamino-4-ethoxypyrrolidinyl group, 3-aminomethyl-4-ethoxypyrrolidinyl group, 3-dimethylaminomethyl-4-ethoxypyrrolidinyl group, 3-amino-4-aminocarbamoylpyrrolidinyl group, 3-amino-4-dimethylaminocarbamoylpyrrolidinyl group, 3-amino-4-hydroxypyrrolidinyl group, 3-amino-4-hydroxymethylpyrrolidinyl group, 3-amino-4-hydroxyethylpyrrolidinyl group; 3-amino-4-methyl-4-hydroxymethylpyrrolidinyl group, 3-aminomethyl-4-hydroxypyrrolidinyl group, 3-dimethylaminomethyl-4-hydroxypyrrolidinyl group, 3,4-dihydroxypyrrolidinyl group, 3,4-dimethoxypyrrolidinyl group, 3-hydroxy-4-methylpyrrolidinyl group, 3-amino-4-fluoropyrrolidinyl group, 3-amino-4-fluoromethylpyrrolidinyl group, 3-amino-4-trifluoromethylpyrrolidinyl group, 3-methylamino-4-fluoropyrrolidinyl group, 3-dimethylamino-4-fluoropyrrolidinyl group, 3-aminomethyl-4-fluoropyrrolidinyl group, 3-methylaminomethyl-4-fluoropyrrolidinyl group, 3-dimethylaminomethyl-4-fluoropyrrolidinyl group; 3-methylamino-4-chloropyrrolidinyl group; 3-aminomethyl-4-chloropyrrolidinyl group, 3-methylaminomethyl-4-chloropyrrolidinyl group, 3-(2-hydroxyethyl) aminomethylpyrrolidinyl group, 3-(2-fluoroethyl) aminometylpyrrolidinyl group, 3-amino-4-methylthiopyrrolidinyl group, 3-amino-4-methyl-sulfinylpyrrolidinyl group, 3-formimidoylaminopyrrolidinyl group, 3-

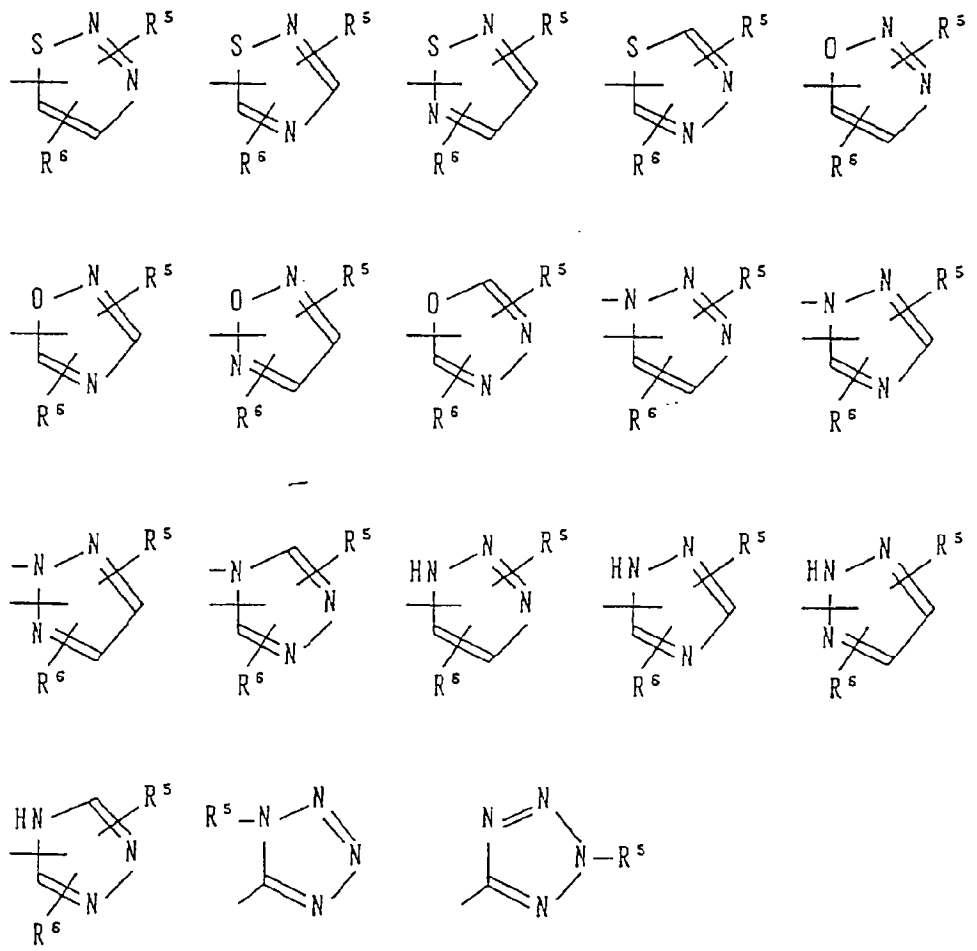
(2-dimethylhydrazino)pyrrolidinyl group, 3-amino-4-methylenepyrrolidinyl group, 3-(t-butoxycarbonyl aminoacetyl)amino-4-methylpyrrolidinyl group, 3-aminoacetylamino-4-methylpyrrolidinyl group, 3-(2-aminopropanoyl)amino-4-methylpyrrolidinyl group, 3-(2-amino-3-phenylpropanoyl)amino-4-methylpyrrolidinyl group, 3-(2-benzyloxycarbonylamino-3-methylbutanoyl)amino-4-methylpyrrolidinyl group, 3-(2-amino-3-methylbutanoyl)amino-4-methylpyrrolidinyl group, 3-(2-amino-2-methylpropanoyl)amino-4-methylpyrrolidinyl group, 7-amino-5-azaspiro[2,4]heptan-5-yl group; piperazinyl group, 4-methylpiperazinyl group, 3-methylpiperazinyl group, 2-methylpiperazinyl group, 3,4-dimethylpiperazinyl group, 3,5-dimethylpiperazinyl group, 3,3-dimethylpiperazinyl group, 3,4,5-trimethylpiperaziny, group, 4-ethoxycarbonylpiperazinyl group, 4-t-butoxycarbonylpiperazinyl group, 4-acetylpiperazinyl group, 4-benzyloxycarbonylpiperazinyl grup, 4-ethylpiperazinyl group, 3,4-diethylpiperazinyl group, 3,4,5-triethylpiperazinyl group, 4-ethyl-3,5-dimethylpiperazinyl group, 3-methyl-4-acetylpiperazinyl group, 3-methyl-4-t-butoxycarbonylpiperazinyl group, 4-benzylpiperazinyl group, 4-n-propylpiperazinyl group; 4-isopropylpiperazinyl group, 4-t-butylpiperazinyl group, 4-cyclopyperazinyl group, 4-cyclopentylpiperazinyl group, 4-cyclopropylmethylpiperazinyl group, 4-phenylpiperazinyl group, 4-(p-dimethylaminophenyl)piperazinyl group, 4-(p-methoxyphenyl)piperazinyl group, 4-(p-fluorophenyl)-piperazinyl group, 3-phenylpiperazinyl group, 3-(p-fluorophenyl)piperazinyl group, 3-(p-chlorophenyl)piperazinyl group, 3-(p-hydroxyphenyl)piperazinyl group, 3-(p-methylphenyl)piperazinyl group, 4-hydroxyethylpiperazinyl group; 4-aminoethylpiperazinyl group, 4-allylpiperazinyl group, 4-cinnamylpiperazinyl group, 4-cyanoethylpiperazinyl group, 4-carboxyethylpiperazinyl group, 4-carboxymethylpiperazinyl group, 4-(1,2-dicarboxyethyl)piperazinyl group, 4-hydroxypiperazinyl group, 3-fluoromethylpiperazinyl group, 3-trifluoromethylpiperazinyl group, 4-formimidoylpiperazinyl group, 4-acetoimidoylpiperazinyl group; piperidino group, 4-amino piperidino group, 4-dimethylaminopiperidino group, 4-hydroxypiperidino group, morpholino group, 2-aminomethylmorpholino group, 2-methylaminomorpholino group, 2-dimethylaminomorpholino group, thiomorpholino group, homopiperazinyl group, 4-methylhomopiperazinyl group, thiazolidinyl goup, and oxazolidinyl group.

Examples of the cyclo- lower alkenyl group represented by Y include unsaturated 5 to 7 membered aliphatic carbocyclic groups, such as cyclopentenyl group, cyclohexenyl group and cyclohexedienyl group. Examples of the cyclo- lower alkenyl groups represented by Y which may have a substituent include oxo-cyclohexenyl group, oxo-cyclopentenyl group, amino-cyclohexenyl group and amino-cyclopentenyl group, among which 3-oxo-cyclohexenyl group, 3-oxo-cyclopentenyl group, 3-amino-cyclohexenyl group and 3-amino-cyclopentenyl group are preferred.

In case where Y is the group represented by the formula R^3-$(CH_2)_m$-A-, groups similar to those capable of substituting the cyclic amino group described above may be mentioned as substitutable groups among the amino groups of R^3 which may have a substituent.

In case where Z is the group represented by the formula C-R^4, the atoms similar to X may be mentioned as the halogen atoms represented by R^4, among which fluorine atom and chlorine atom are preferred.

Example of the five-membered heterocyclic group represented by W which has 3 or more hetero atoms, among which at least 2 hetero-atoms are nitrogen atoms include saturated or unsaturated five-membered heterocyclic group which has two nitrogen atoms and a hetero-atom selected from the group consisting of nitrogen, oxygen and sulfur. The heterocyclic group represented by W may be substituted with a suitable substituent such as amino group, above-mentioned substituted amino group, oxo group or the like. Preferable examples of such substituents are as follows:



Examples of the two kinds of substituents R^5 and R^6 in W individually include a hydrogen atom, a lower alkyl group similar to R^2, and halo lower alkyl groups such as fluoromethyl, trifluoromethyl and fluoroethyl.

Preferable examples of the group represented by W include: 1,2,3-thiadiazole-4-yl, 5-methyl-1,2,3-thiadiazole-4-yl, 1,3,4-thiadiazole-2-yl, 5-methyl-1,3,4-thiadiazole-2-yl, 5-trifluoromethyl-1,3,4-thiadiazole-2-yl, 1,2,3-thiadiazole-5-yl, 4-methyl-1,2,3-thiadiazole-5-yl, 1,2,4-thiadiazole-3-yl, 5-methyl-1,2,4-thiadiazole-3-yl, 1,2,4-thiadiazole-5-yl, 3-methyl-1,2,4-thiadiazole-5-yl, 1,2,5-thiadiazole-3-yl, 4-methyl-1,2,5-thiadiazole-3-yl, 4-fluoromethyl-1,2,5-thiadiazole-3-yl, 1,2,3-triazole-4-yl, 1-methyl-1,2,3-triazole-5-yl, 1,2,4-triazole-4-yl, 3-methyl-1,2,4-triazole-4-yl, 1,2,4-triazole-3-yl, 1-methyl-1,2,4-triazole-5-yl, 1-benzyl-1,2,4-triazole-3-yl, 1,2,4-triazole-5-yl, 2-methyl-1,2,4-triazole-5-yl, 2-benzyl-1,2,4-triazole-5-yl, 3,5-dimethyl-1,2,4-triazole-4-yl, 1,2,3-oxadiazole-4-yl, 5-methyl-1,2,3-oxadiazole-4-yl, 1,3,4-oxadiazole-2-yl, 5-methyl-1,3,4-oxadiazole-2-yl, 5-trifluoromethyl-1,3,4-oxadiazole-2-yl, 1,2,3-oxadiazole-5-yl, 4-methyl-1,2,3-oxadiazole-5-yl, 1,2,4-oxadiazole-3-yl, 5-methyl-1,2,4-oxadiazole-3-yl, 1,2,4-oxadiazole-5-yl, 3-methyl-1,2,4-oxadiazole-5-yl, 1,2,5-oxadiazole-3-yl, 4-methyl-1,2,5-oxadiazole-3-yl, tetrazole-5-yl, 1-methyl-tetrazole-5-yl, 2-methyl-tetrazole-5-yl, 1,2,5-thiadiazole-3-ylmethyl, and 1,2,3-thiadiazole-4-ylmethyl.

The quinolone derivatives or salts thereof of formula (1) can be converted into both of acid addition salts and base addition salts, and the salts include those forming chelate salts with boron compounds. Examples of acid addition salts include: (a) salts with mineral acids such as hydrochloric acid and sulfuric acid; (b) salts with organic carboxylic acids such as formic acid, citric acid, trichloroacetic acid, trifluoroacetic acid, fumaric acid and maleic acid; and (c) salts with sulfonic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, mesitylenesulfonic acid and naphthalenesulfonic acid. On the other hand, examples of base addition salts include: (a') salts with alkali metals such as sodium and potassium; (b') salts with alkaline earth metals such as calcium and magnesium; (c') ammonium salts; and

(d') salts with nitrogen-containing organic bases such as trimethylamine, triethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, diethylamine, cyclohexylamine, procaine, dibenzylamine, N-benzyl-beta-phenethylamine, 1-ephenamine and N,N'-dibenzylethylenediamine. Examples of boron compounds include boron halides such as boron fluoride, and lower acyloxy borons such as acetoxy boron,

The quinolone derivatives or salts thereof of formula (1) may be not only in unsolvated forms but also in hydrated or solvated forms. The present invention therefore embraces the compounds (1) in any crystalline forms and their hydrated and solvated products.

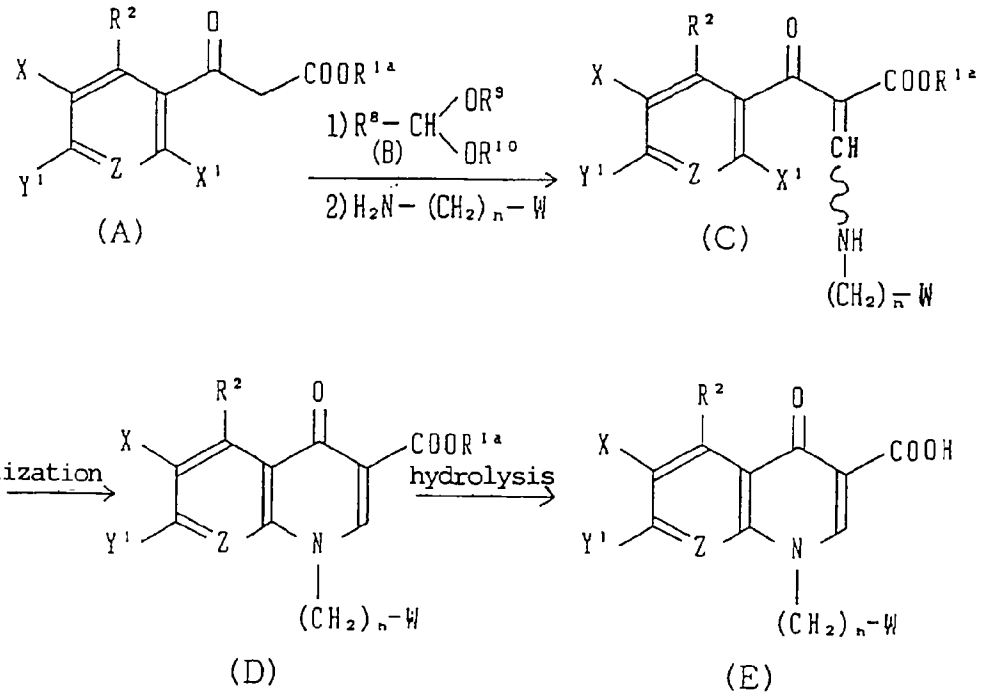
The quinolone derivatives or salts thereof of formula (1) include those containing an asymmetric carbon atom which can exist as optically active substances. These optically active substances are also embraced in the compounds of the present invention. The compounds of formula (1) further include those containing two or more asymmetric carbon atoms which can exist as different stereoisomers (cis-form and trans-form). These stereoisomers are also included in the compounds of the present invention.

Each of the quinolone derivatives or salts thereof of formula (1) can be prepared by a process suited for the types of its substituent groups. Preferred preparation processes are as follows.

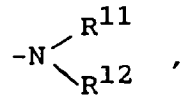
Process 1:

Among the compounds represented by formula (1), those in which R^1 is a hydrogen atom or a lower alkyl group and Y is a halogen atom can be prepared, for example, by the series of steps shown in the following reaction scheme (1):

Reaction Scheme (1):



wherein X^1 and Y^1 individually represent a halogen atom; R^{1a} represents a lower alkyl group; R^8 represents a lower alkoxy group or a group



wherein R^{11} and R^{12} individually represent a lower alkyl group; R^9 and R^{10} individually represent a lower alkyl group; and X, Z, W, R^2 and n have the same meaning as defined above.

Namely, the compound (C) can be obtained by reacting the compound (A) with an orthoformic acid ester (B) such as ethyl orthoformate or methyl orthoformate in acetic anhydride, and then reacting the resulting product with the compound H_2N-$(CH_2)_n$-W. The reaction between the compound (A) and the orthoformic acid ester is conducted generally at 0-160 °C, preferably at 50-150 °C. The reaction time is generally from 10 minutes to 48 hours, preferably from 1 hour to 10 hours. The orthoformic acid ester (B) can be used in at least an equimolar amount, preferably in a molar amount about 1 to 10 times relative to the compound (A).

The subsequent reaction with the compound H_2N-$(CH_2)_n$-W is conducted in a suitable solvent. Any solvent can be used here, as long as it does not affect the reaction. Examples of such solvents include: aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as diethyl ether, tetrahydrofuran, dioxane, monoglyme and diglyme; aliphatic hydrocarbons such as pentane, hexane, heptane and ligroin; halogenated hydrocarbons such as methylene chloride, chloroform and carbon tetrachloride; dipolar aprotic solvents such as dimethylformamide and dimethylsulfoxide; and alcohols such as methanol, ethanol and propanol. This reaction is conducted generally at 0-150 °C, preferably at 0-100 °C. The reaction time generally ranges from 10 minutes to 48 hours. The compound H_2N-$(CH_2)_n$-W can be used in at least an equimolar amount, preferably in a molar amount 1-2 times relative to the compound (A).

As an alternative, the compound (C) may be obtained by a reaction of the compound (A) with an acetal such as N,N-dimethylformamide dimethyl acetal or N,N-dimethylformamide diethyl acetal, followed by a reaction with the compound H_2N-$(CH_2)_n$-W. Any solvent may be used for the reaction with the acetal, as long as it is inert to the reaction. The above-mentioned solvents can be used as such inert solvent. This reaction is conducted generally at 0-150 °C, preferably at room temperature to 100 °C. The reaction time is generally from 10 minutes to 48 hours, preferably from 1 to 10 hours.

The compound (C) thus obtained is subjected to cyclization reaction to obtain compound (D). This reaction is conducted in a suitable solvent in the presence of a basic compound. Any solvent can be used for this reaction, as long as it does not affect the reaction. Examples of such solvents include: aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as diethyl ether, tetrahydrofuran, dioxane and monoglyme; halogenated hydrocarbons such as methylene chloride, chloroform and carbon tetrachloride; alcohols such as methanol, ethanol, propanol and butanol; dipolar aprotic solvents such as dimethylformamide and dimethylsulfoxide. Preferable examples of basic compounds include: alkali metals such as metallic sodium and metallic potassium; metal hydrides such as sodium hydride and calcium hydride; inorganic bases such as sodium hydroxide, potassium hydroxide and sodium carbonate; alkoxides such as sodium methoxide, sodium ethoxide and potassium-t-butoxide; metal fluorides such as potassium fluoride and sodium fluoride; and organic bases such as triethylamine and 1,8-diazabicyclo [5.4.0]-undecene (DBU). This reaction is conducted generally at 0-200 °C, preferably from room temperature to 180 °C. The reaction can be brought to completion usually in 5 minutes to 24 hours. The basic compound may be used in at least an equimolar amount, preferably in a molar amount 1-2 times relative to the compound (C).

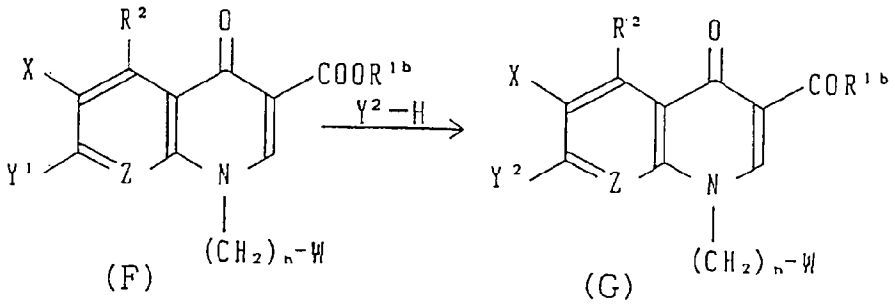
If desired, the compound (D) thus obtained is further subjected to hydrolysis to obtain compound (E). This reaction can be conducted under reaction conditions which are employed in usual hydrolysis reactions. For example, the hydrolysis reaction is carried out in the presence of a basic compound such as sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate; a mineral acid such as hydrochloric acid, sulfuric acid or hydrobromic acid; or an organic acid such as p-toluenesulfonic acid, and in a solvent, e.g. water; an alcohol such as methanol, ethanol or propanol; an ether such as tetrahydrofuran or dioxane; a ketone such as acetone or methyl ethyl ketone; or an acetic acid; or a mixed solvent thereof. This reaction is conducted generally at room temperature to 180 °C, preferably from room temperature to 140 °C. The reaction time generally ranges from 1 hour to 24 hours.

Process 2:

Among the compounds represented by formula (1), those in which R^1 is a hydrogen atom or a lower alkyl group; and Y is a cyclic amino group which may have a substituent, a cyclo lower alkenyl group which

may have a substituent, or a group R^3-$(CH_2)_m$-A-, wherein R^3, A and m have the same meaning as defined above, can be produced by the steps shown in the following reaction scheme (2):

Reaction Scheme (2):



wherein X^{1b} represents a halogen atom or a lower alkyl group, Y^2 is a cyclic amino group which may have a substituent, a cyclo lower alkenyl group which may have a substituent or a group R^3-$(CH_2)_m$-A-, wherein R^3, A and m have the same meaning as defined above, and R^2, X, Y^1, W and n have the same meaning as defined above.

Namely, the compound (F) obtained in the process 1 is reacted with the compound represented by the formula Y^2-H to obtain compound (G).

This reaction is carried out in a suitable solvent at room temperature to 160 °C, if desired, in the presence of an acid-neutralizing agent such as sodium carbonate, calcium carbonate, sodium hydrogencarbonate, triethylamine or 1,8-diazabicyclo [5.4.0]-undecene (DBU). Examples of solvents which are usable in this reaction include: aromatic hydrocarbons such as benzene, toluene and xylene; alcohols such as methanol and ethanol; ethers such as tetrahydrofuran, dioxane and monoglyme; halogenated hydrocarbons such as methylene chloride, chloroform and carbon tetrachloride; dipolar aprotic solvents such as dimethylformamide and dimethylsulfoxide; and other solvents which do not adversely affect the reaction such as acetonitrile and pyridine. The reaction can generally be brought to completion in a few minutes to 48 hours, preferably from 10 minutes to 24 hours. The compound Y^2-H may be used in at least an equimolar amount, preferably in a molar amount 1-5 times relative to the compound (F).

In cases where the R^{1b} of the compound (G) is a lower alkyl group, the group may be substituted with a hydrogen atom by hydrolysis.

When the starting compounds used in the processes 1 and 2 contain one or more reactive groups which do not take part in the reactions, such as amino group, imino group, hydroxyl group, mercapto group or carboxyl group, these starting compouds may be used in a form with these groups being protected. In such case, the protective groups are removed in a general manner after the completion of the reaction. Any group can be used as the protective group, as long as it can be removed without destroying the structure of the compound of the present invention to be formed by the reaction. Groups usually employed in the chemical field of peptides, aminosacchaides and nucleic acids can be used.

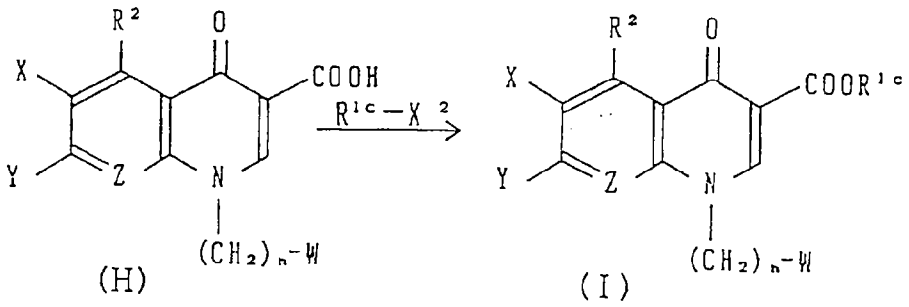
The starting compound (A) can be prepared by one of the processes described in the following documents or by a similar process:

1) J. Heterocyclic Chem. 22, 1033 (1985)
2) Liebigs Ann. Chem. 29 (1987)
3) J. Med. Chem. 31, 911 (1988)
4) J. Org. Chem. 35, 930 (1970)
5) Japanese Patent Application Laid-open (Kokai) No. 246541/1987
6) Japanese Patent Application Laid-open (Kokai) No. 26272/1987
7) Japanese Patent Application Laid-open (Kokai) No. 145268/1988
8) J. Med. Chem. 29, 2363 (1986)
9) J. Fluorin Chem. 28, 361 (1985)
10) Japanese Patent Application Laid-open (Kokai) No. 198664/1988
11) Japanese Patent Application Laid-open (Kokai) No. 264461/1988
12) Japanese Patent Application Laid-open (Kokai) No. 104974/1988

13) European Patent Application No. 230948
14) Japanese Patent Application Laid-open (Kokai) No. 282384/1990
15) Japanese Kohyo Publication No. 502452/1991
16) J. Het. Chem. 27, 1609 (1990)

Process 3:

Among the compounds represented by formula (1), those in which R^1 is a carboxy protective group can be prepared by the steps shown in the following reaction scheme (3): Reaction Scheme (3):



wherein R^{1c} represents a carboxy protective group, X^2 represents a halogen atom, and R^2, X, Y, Z, W and n have the same meaning as defined above.

Compound (I) is obtained by reacting the compound (H) with the halogen compound R^{1c}-X^2. Examples of the preferred solvents include: aromatic hydrocarbons such as benzene and toluene; halogenated hydrocarbons such as methylene chloride and chloroform; dipolar aprotic solvents such as dimethylformamide and dimethyl sulfoxide; and other inactive solvents such as acetonitrile. The reaction is carried out at room temperature to 100 °C. It is preferred that this reaction be carried out in the presence of a basic compound such as triethylamine, diisopropylethylamine, dicyclohexylamine, DBU, sodium carbonate, potassium carbonate or sodium hydroxide.

Among the compounds represented by the formula (1), those containing a primary or secondary amino group as heterocyclic group indicated by Y can be converted to the compounds which have a formimidoyl group or lower alkylimdoyl group on the amino group by reacting with formimidic acid ester or lower alkanecarboximidic acid ester.

The compounds of the present invention thus obtained are isolated and purified by methods known per se in the art. They are obtained in the form of salts, free carboxylic acids or free amines, depending on the conditions for isolation and purification. However, they can be converted mutually from one of these forms into another one, whereby the compounds of the present invention can be prepared in a desired form.

When the compounds (1) of the present invention are used as antibacterial agents, the compositions can be treated as compositions together with pharmaceutical allowable carriers for parenteral dosage such as injection, per rectum, eye instillation and the like and oral administration in the form of solid and solution.

Relating to the form of the composition for injection, pharmaceutical allowable axenic water or nonaqueous solution, suspension or emulsion and the like are give. As examples of appropriate nonaqueous carrier, diluent, solution or vehicle, propylene glycol, polyethylene glycol and vegetable oils such as olive oil and injectable organic esters including, for example, oleic acid ethyl are given. There compositions may include supplementary agents such as antiseptics, wetting agents, emulsifiers, dispersants and the like. The compositions, for example, can be sterilized by filtering with a bacteria holding filter or by mixing with a sterilizer in the form of an axenic solid composition soluble in sterilized water or other several sterilized injectable solutes or media right before the use.

The preparation for eye instillation dosage can preferably include dissolution adjuvants, preservatives, isotonic agents, mucilages and the like.

The solid preparations for oral dosage can include capsules, tablets, pills, powders and granules. In preparing the solid preparations, generally, the compound of the present invention is mixed with at least one kind of an inert diluent such as sucrose, lactose or starch. In a usual preparation, the preparations can further include a supplementary material except the inert diluent, for example, a lubricant such as magnesium stealate or the like. Further, the capsules, tablets and pills can further include a buffer. The

tablets and pills can further apply an enteric coat thereon.

The solution preparations for oral dosage can include inert diluents usually used by a person skilled in the art, for instance, pharmaceutical allowable emulsifiers including water, solutions, suspensions, syrups and elixirs. In addition to such inert diluents, the compositions can be blended with supplementary agents such as wetting agents, emulsifiers, suspensions, edulcorants, flavors and perfumes.

The preparations for per rectum dosage may preferably include excipients such as cocoa butter or suppository wax in addition to the compound of the present invention.

The dose of the compound represented by general formula (1) depends on the properties of the compound to be dosed, dosing route, the desired treating period and other factors, and is, in general, approximately 0.1 to 1000 mg/kg a day, and preferably approximately 1 to 100 mg/kg a day. If necessary, this dose for one day can be divided into 2-4 times.

Example 1

Ethyl 3-(1,2,5-thiadiazol-3-yl-amino)-2-(2,6-dichloro-5-fuluoronicotinoyl)acrylate (Compound No.1):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (5.4g), triethyl orthoformate (4.8ml) and acetic anhydride (5.5ml) was stirred at 130 °C for 2 hours. After the solvent was removed in vacuo, a solution of 3-amino-1,2,5-thiadiazole hydrochloride (2.75g) and triethylamine (2g) in chloroform (20ml) was added to the residue. The mixture was stirred at room temperature for 20 hours. The solvent was removed in vacuo. The residue was purified by chromatography on silicagel (chloroform as an eluent). The title compound No. 1 was obtained as a yellow oil (6.8g).

^{1}H-NMR($CDCl_3$) δ;

0.96 and 1.17(t,J = 7Hz,3H), 4.16(q,J = 7Hz,2H),

7.43 and 7.56(d,J = 7Hz,1H),

8.33 and 8.38(s,1H),

8.95 and 9.03(d,J = 12.5Hz,1H)

Example 2

Ethyl 7-chloro-6-fluoro-1-(1,2,5-thiadiazol-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.2):

To a solution of compound No.1 (6.8g) in tetrahydrofuran (200ml), 0.7g of sodium hydride (60% in oil) was added with ice cooling. Then the solution was stirred for 1 hour at the same temperature. After addition of aqueous 5% citric acid solution (50ml), tetrahydrofuran was removed in vacuo. The aqueous solution was extracted with chloroform (200ml). The organic phase was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. To the residue was added diisopropylether and filtrated. The title compound No. 2 was obtained as a yellow solid (5.2g).

Melting point: 175-178 °C

^{1}H-NMR($CDCl_3$) δ;

1.43(t,J = 7Hz,3H), 4.43(q,J = 7Hz,2H), 8.54(d,J = 6.9Hz,1H), 9.26(s,1H), 9.27(s,1H)

Example 3

7-Chloro-6-fluoro-1-(1,2,5-thiadiazol-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.3):

Compound No.2 (5g) was dissolved in acetic acid (50ml) and 6N-HCl (20ml). The solution was stirred at 100 °C for 0.5 hour. After cooling, the precipitate was filtrated and washed with water, ethanol and ether. The title compound No. 3 was obtained as pale yellow needles (4.5g).

Melting point: 222-223 °C

^{1}H-NMR(DMSO-d_6) δ;

8.8(d,J = 7.8Hz,1H), 9.24(s,1H), 9.26(s,1H)

Example 4

6-Fluoro-7-(pyrrolidin-1-yl)-1-(1,2,5-thiadiazole-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.4):

A mixture of compound No.3 (80mg), pyrrolidine (21mg) and triethylamine (50mg) in acetonitrile (5ml) was stirred at 80 °C for 30 minutes. After cooling, the precipitate was filtrated and washed with ethanol and diisopropylether successively. The title compound No. 4 was obtained as a pale yellow solid (85mg).

Melting point: 269-273 °C

^{1}H-NMR($CDCl_3$) δ;

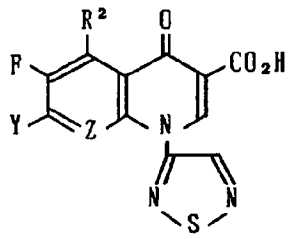
1.9-2.1(m,4H), 3.7(brs,4H), 8.0(d,J = 12.8Hz,1H), 9.12(s,1H), 9.18(s,1H)

Example 5

Compounds Nos. 5-11 listed in Tables 1 and 2 were prepared in a similar manner to Example 4. The data are also shown in Tables 1-2.

Table 1

Compound:



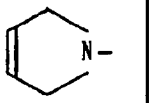
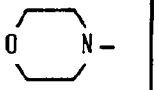
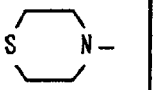
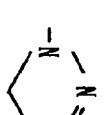
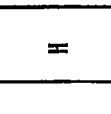
Compound No.	Group			Property	Melting point (℃)	^{1}H-NMR	Solvent
	R^2	Y	Z				
5	H		N	Pale yellow solid	274 ~ 276	[$CDCl_3$+DMSO-d_6] δ ; 4.25-4.45(m, 2H), 4.65-4.85(m, 2H), 5.95(s, 2H), 8.1(d, J=12.4Hz, 1H), 9.17(s, 1H), 9.18(s, 1H)	CH_3CN
6	H		N	Colorless solid	254 ~ 257	[$CDCl_3$+DMSO-d_6] δ ; 3.65-3.85(m, 8H), 8.15(d, J=13.3Hz, 1H), 9.03(s, 1H), 9.11(s, 1H)	CH_3CN
7	H		N	Pale yellow solid	244 ~ 246	[$CDCl_3$] δ ; 2.65-2.8(m, 4H), 4.0-4.1(m, 4H), 8.15(d, J=13.3Hz, 1H), 9.0(s, 1H), 9.1(s, 1H)	CH_3CN

Table 2

Compound No.	Group			Property	Melting point (℃)	^{1}H-NMR	Solvent
	R^2	Y	Z				
8	H		N	Red solid	288 ~ 292	[DMSO-d_6] δ ; 2.85-3.0(m,2H), 3.8-3.9(m,2H), 7.47(s,1H), 8.19(d,J=12.4Hz,1H), 9.06(s,1H), 9.4(s,1H)	CH_3CN
9	H		N	Pale yellow solid	233 ~ 236	[DMSO-d_6] δ ; 7.22(s,1H), 7.74(s,1H), 8.39(s,1H), 8.88(d,J=10.2Hz,1H), 9.23(s,1H), 9.4(s,1H)	CH_3CN
10	H		N	Colorless solid	238.5 ~ 239.5	[DMSO-d_6] δ ; 3.05-3.2(m,2H), 3.92(brs,2H), 4.73(s,2H), 8.17(d,J=12.8Hz,1H), 9.0(s,1H), 9.35(s,1H)	CH_3CN
11	H		N	Pale ocher solid	217 ~ 219	[DMSO-d_6] δ ; 1.91(brs,2H), 4.36(brs,1H), 5.09(brs,1H) 8.04(d,J=12.7Hz,1H), 8.96(s,1H), 9.33(s,1H)	CH_3CN Et_3N

Example 6

6-Fluoro-7-(7-amino-5-azaspiro[2.4]heptan-5-yl)-1-(1,2,5-thiadiazol-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrochloride (Compound No.12):

A mixture of compound No.3 (114mg), triethylamine (70mg) and 7-t-buthoxycarbonylamino-5-azaspiro-[2.4]heptane (90mg) in acetonitrile (5ml) was stirred at 80 °C for 10 minutes. After the solvent was removed in vacuo, the residue was extracted with chloroform (50ml). The organic layer was washed with 5% aqueous citric acid solution and water successively, then dried. After the solvent was removed in vacuo, 4N-HCl/1,4-dioxane (5ml) was added to the residue. The solution was stirred at room temperature for 1 hour. The precipitate was collected by filtration. The title compound No. 12 was obtained as a yellow solid (110mg).

Melting point: 216-221.5 °C

^{1}H-NMR(DMSO-d_6) δ;

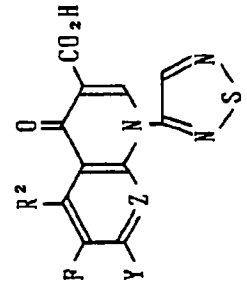
0.7-1.0(m,3H), 1.0-1.2(m,1H), 3.8-4.4(m,3H), 8.16(d,J = 12.2Hz,1H), 8.35(brs,3H), 9.0(s,1H), 9.36(s,1H)

Example 7

Compounds Nos. 13 and 14 listed in Table 3 were prepared in a similar manner to Example 6. The results are also shown in Table 3.

Table 3

Compound:



Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
13	H	H_2N ·HCl isomer A	N	Yellow solid	215 ~ 220.5	[DMSO-d_6] δ; 0.7-1.0(m,3H), 1.0-1.2(m,1H), 3.7-4.4(m,3H), 8.16(d,J=12.4Hz,1H), 8.35(brs,3H), 9.0(s,1H), 9.36(s,1H)	CH_3CN ↓ 4N-HCl /1,4-dioxane
14	H	H_2N ·HCl isomer B	N	Yellow solid	217 ~ 224	[DMSO-d_6] δ; 0.7-1.0(m,3H), 1.0-1.2(m,1H), 3.7-4.3(m,3H), 8.16(d,J=12.2Hz,1H), 8.37(brs,3H), 9.0(s,1H), 9.36(s,1H)	CH_3CN ↓ 4N-HCl /1,4-dioxane

Example 8

6-Fluoro-7-(2-aminoethylthio)-1-(1,2,5-thiadiazole-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrochloride (Compound No.15):

A mixture of compound No.3 (100mg), triethylamine (60mg) and 2-t-buthoxycarbonylaminoethanethiol (71mg) in acetonitrile (5ml) was stirred at room temperature for 30 minutes. The precipitate was collected by filtration and dissolved in acetic acid (1ml) and 6N-HCl(1ml). After stirring at 100 °C for 20 minutes, 5ml of water was added to this solution. The precipitate was collected by filtration and washed with ethanol, chloroform and ether successively. The title compound No. 15 was obtained as a colorless solid (70mg).

Melting point: Colored and decomposed at 269 °C or more

^{1}H-NMR(DMSO-d_6) δ;

2.84(brs,2H), 3.3(brs,2H), 8.14(brs,3H), 8.47(d,J = 9.0Hz,1H), 9.19(s,1H), 9.33(s,1H)

Example 9

7-(3-Amino-1-cyclohexen-1-yl)-6-fluoro-1-(1,2,5-thiadiazol-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylicacid hydrochloride (Compound No.16):

The compound No.2 (200mg) obtained in Example 2, bistriphenylphosphine-palladium(II)chloride (10mg) and 2,6-di-t-butyl-4-methylphenol (2 pieces of crystal) were dissolved in N,N-dimethylformamide (2ml). 300mg of 3-t-buthoxycarbonylamino-1-tri-n-butylstannyl-1-cyclohexene were added thereto at 85 °C during 20 minutes. After stirring at 100 °C for 1.5 hours, the solvent was removed, the residue was added with hexane (10ml) and filtrated. The collected solid matter was purified by chromatography on silicagel-(chloroform/ethylacetate 10:1). The pale yellow solid (100mg) which was obtained was dissolved in a mixture of acetic acid (1ml) and 6N-HCl (1ml), then this solution was stirred at 100 °C for 30 minutes. After evaporation of the solvent, 5ml of ethanol was added. The precipitate was collected by filtration and washed with diisopropylether. The title compound No. 16 was obtained as a yellow solid (30mg).

Melting point: Colored and decomposed at 235 °C or more

^{1}H-NMR(DMSO-d_6) δ;

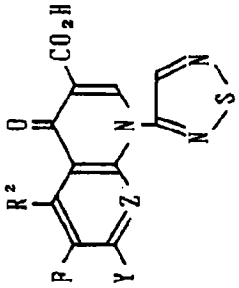
1.5-1.8(m,2H), 1.8-2.1(m,2H), 2.36(brs,2H), 4.04(brs,1H), 6.8(s,1H), 8.35(brs,3H), 8.63(d,J = 10.7Hz,1H), 9.25(brs,2H)

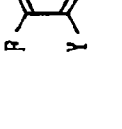
Example 10

Compound No.17 listed in Table 4 was synthesized in a similar manner to Example 9. The data are also shown in Table 4.

Table 4

Compound:



Compound No.	Group			Property	Melting point (℃)	^{1}H-NMR	Soluent
	R^2	Y	Z				
17	H		N	Yellow solid	188 ~ 195	[CDCl$_3$] δ: 2.1-2.3(m, 2H), 2.5-2.65(m, 2H), 2.7-2.8(m, 2H), 6.84(s, 1H), 8.6(d, J=9.8Hz, 1H), 9.12(s, 1H), 9.46(s, 1H)	DMF

Example 11

7-(3-(S)-Aminopyrrolidin-1-yl)-6-fluoro-1-(1,2,5-thiadiazol-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrochloride (Compound No.18):

A mixture of compound No.3 (1.5g), triethylamine (1.06g) and 3-(S)-aminopyrrolidine (0.46g) in acetonitrile (150ml) was stirred at 80 °C for 60 minutes. After cooling, the precipitate was filtrated and washed with ethanol (5ml), then dissolved in 10ml of c-HCl and stirred for 10 minutes. After the solvent was evaporated, ethanol (10ml) was added for filtration. A yellow solid of the title compound was obtained (1.6g). Crystallization from ethanol-water yielded the title compound No. 18 in pale yellow needles (1.5g).

Melting point: Colored from 235 °C, and melted at 257-260 °C

^{1}H-NMR(DMSO-d6) δ;

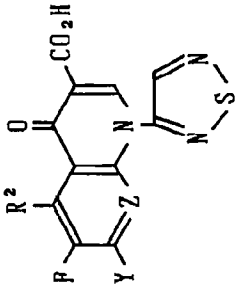
2.5(brs,1H), 2.51(brs,1H), 8.13(d,J = 12.7Hz,1H), 8.0-8.8(br,3H), 9.00(s,1H), 9.33(s,1H)

Example 12

Compounds Nos. 19-31 listed in Tables 5-8 were synthesized in a similar manner to Example 11. The data are also shown in Tables 5-8.

Table 5

Compound:



Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
19	H	H_2N, Me, N, Cis— (—) · HCl	N	Pale yellow needles	241 ~ 243	[DMSO-d_6] δ ; 1.10(d, J=6.8Hz, 3H), 2.5-2.7(m, 1H), 8.13(d, J=12.7Hz, 1H), 8.4(brs, 3H), 8.99(s, 1H), 9.35(s, 1H)	MeCN Et_3N
20	H	NH_2, N, (3R, 1S) · HCl	N	Pale ocher solid	255 ~ 260	[DMSO-d_6] δ ; 1.26(d, J=6.4Hz, 3H), 1.70(brs, 1H), 2.04(brs, 1H), 2.45(brs, 1H), 8.07(d, J=12.7Hz, 1H), 8.23(brs, 3H), 8.97(s, 1H), 9.36(s, 1H)	〃

Table 6

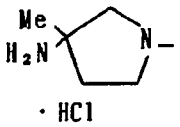
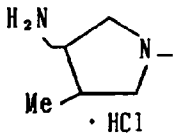
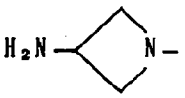
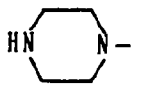
Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
21	H	 · HCl	N	Pale yellow solid	257 ~ 259	[DMSO-d_6] δ ; 1.46(s, 3H), 2.09(brs, 1H), 2.25(brs, 1H), 8.14(d, J=12.2Hz, 1H), 9.00(s, 1H), 9.36(s, 1H)	MeCN Et_3N
22	H	 · HCl Cis form	N	Pale orange solid	207 ~ 213	[DMSO-d_6] δ ; 0.93(d, J=6.35Hz, 3H), 2.91(brs, 2H), 8.10(brs, 1H), 8.0-8.9(br, 3H), 8.98(s, 1H), 9.42(s, 1H)	〃
23	H	 · HCl	N	Pale yellow solid	250 ~ 260 Decomposed	[DMSO-d_6] δ ; 3.8-4.0(m, 2H), 8.16(d, J=11.2Hz, 1H), 8.62(brs, 3H), 9.03(s, 1H), 9.30(s, 1H)	〃
24	H	 · HCl	N	Pale yellow solid	268 ~ 275 Decomposed	[DMSO-d_6] δ ; 3.48(s, 4H), 3.86(s, 4H), 8.27(d, J=13.2Hz, 1H), 9.04(s, 1H), 9.32(s, 1H), 9.1-9.8(br, 2H)	〃

Table 7

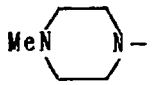
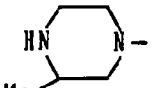
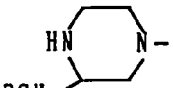
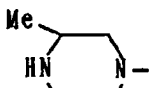
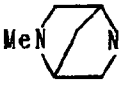
Compound No	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
25	H	 · HCl	N	Pale yellow solid	Colored from 240℃, decomposed	[DMSO-d_6+D_2O] δ ; 2.82(s, 3H), 8.24(d, J=13.2Hz, 1H), 9.01(s, 1H), 9.27(s, 1H)	CH_3CN Et_3N
26	H	 (S) · HCl	N	Colorless solid	Colored from 268℃, decomposed	[DMSO-d_6] δ ; 1.2(d, J=6.4Hz, 3H), 3.0-3.15(m, 1H), 3.45-3.6(m, 1H), 4.1-4.3(m, 2H), 8.27(d, J=13.2Hz, 1H), 9.04(s, 1H), 9.31(s, 1H), 9.4-9.7(br, 2H)	〃
27	H	 (R) · HCl	N	Colorless solid	251 ~ 253	[DMSO-d_6] δ ; 3.1-3.3(m, 2H), 3.5-3.8(m, 2H), 4.15-4.32(m, 2H), 4.6(brs, 1H), 4.8(brs, 1H), 8.3(d, J=13.2Hz, 1H), 9.05(s, 1H), 9.32(s, 1H), 9.9(brs, 1H)	〃
28	H	 Cis · HCl	N	Colorless solid	Colored from 292℃, decomposed	[DMSO-d_6] δ ; 1.22(d, J=7.3Hz, 6H), 3.15-3.5(m, 4H), 4.22(d, J=12.7Hz, 2H), 8.27(d, J=12.7Hz, 1H), 9.05(s, 1H), 9.32(s, 1H), 9.7(brs, 1H)	〃

Table 8

Compound No.	Group			Property	Melting point (℃)	^{1}H-NMR	Solvent
	R^2	Y	Z				
29	H	 · HCl (1R, 4R)	N	Pale yellow solid	Colored from 259℃, decomposed	[DMSO-d_6] δ ; 1.9-2.2(m, 2H), 4.48(s, 1H) 8.2(d, J=12.2Hz, 1H), 9.01(s, 1H), 9.26(brs, 1H), 9.31(s, 1H), 9.71(brs, 1H)	CH_3CN Et_3N
30	H	 · HCl (1R, 4R)	N	Colorless solid	Colored from 277℃, decomposed	[DMSO-d_6] δ ; 2.0-2.2(brs, 1H), 2.3-2.5(brs, 1H), 2.83(s, 3H), 3.05-3.2(m, 1H), 3.6-3.9(br, 1H), 4.44(s, 1H), 8.20(d, J=12.2Hz, 1H), 9.0(s, 1H), 9.33(s, 1H), 11.1(brs, 1H)	〃
31	H	 · HCl	N	Colorless solid	Colored from 278℃, decomposed	[DMSO-d_6] δ ; 1.8-2.0(m, 4H), 3.5-3.6(m, 2H), 4.0-4.15(m, 4H), 8.26(d, J=13.2Hz, 1H), 9.03(s, 1H), 9.30(s, 1H), 9.4-9.9(br, 1H)	〃

Example 13

Ethyl 3-(1,2,5-thiadiazol-3-yl-amino)-2-(2,3,4,5-tetrafluorobenzoyl)acrylate (Compound No.32):

A mixture of ethyl 2,3,4,5-tetrafluorobenzoylacetate(2.64g), ethyl orthoformate(2.5ml) and acetic anhydride(2.8ml) was stirred at 130 °C for 6 hours. After the solvent was removed in vacuo, a solution of 3-amino-1,2,5-thiadiazole hydrochloride (1.38g) and triethylamine(1g) in benzene(20ml) was added to the residue. The mixture was stirred at room temperature for 2 hours. The solvent was removed in vacuo. The residue was purified by chromatography on silicagel(chloroform/ethyl acetate 50:1 as an eluent). The title compound N0. 32 was obtained as a yellow solid (3.7g).

Melting point: 81-83 °C

^{1}H-NMR($CDCl_3$) δ;1.06 and 1.22 (t,J = 7Hz,3H) 4.15 and 4.18 (q,J = 7Hz,2H) 7.05-7.2 and 7.25-7.4 (m,1H) 8.31 and 8.36 (s,1H) 8.74 and 8.95 (d,J = 12.2Hz,1H)

Example 14

Ethyl 1-(1,2,5-thiadiazol-3-yl)-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.33):

To a solution of compound No.32 (3.7g) in tetrahydrofuran (100ml), 0.4g of sodium hydride (60% in oil) was added with ice cooling over 20 minutes. Then the solution was stirred for 20 minutes at room temperature. After addition of 5% aqueous citric acid solution (10ml), tetrahydrofuran was removed in vacuo. The aqueous solution was extracted with chloroform (100ml). The organic phase was washed with water, dried ($MgSO_4$) and evaporated. The residue was added with diisopropylether and the solid matter was collected by filtration. The title compound No. 33 was obtained as a colorless solid (2.7g).

Melting point: 167-169 °C

^{1}H-NMR($CDCl_3$) δ;

1.39(t,J = 7Hz,3H), 4.39(q,J = 7Hz,2H), 8.1-8.25(m,1H), 8.48(s,1H), 8.72(s,1H)

Example 15

1-(1,2,5-Thiadiazol-3-yl)-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.34):

Compound No.33 (2.7g) was dissolved in acetic acid (25ml) and 6N-HCl (10ml). The solution was stirred at 100 °C for 0.5 hour. After cooling, the precipitate was filtrated and washed with water, ethanol and ether successively. The title compound No. 34 was obtained as a colorless solid (2.3g).

Melting point: 205-207 °C

^{1}H-NMR(DMSO-d_6) δ;

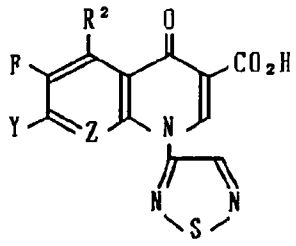
8.15-8.3(m,1H), 9.07(s,1H), 9.23(s,1H)

Example 16

Compounds Nos. 35-39 listed in Tables 9 and 10 were prepared in a similar manner to Example 11, starting from compound No.34 and indicated amines. The results are shown in Tables 9 and 10.

Table 9

Compound :



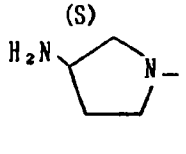
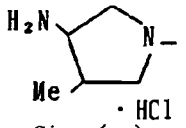
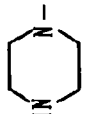
Compound No.	Group			Property	Melting point (℃)	^{1}H-NMR	Solvent
	R^2	Y	Z				
35	H	 · HCl	C–F	Ocher solid	206 ~ 212	[DMSO-d_6] δ ; 1.92-2.09(m, 1H), 2.09-2.27(m, 1H), 3.6-4.0(m, 4H), 7.85(d, J=13.7Hz, 1H), 8.42(brs, 3H), 8.90(s, 1H), 9.22(s, 1H)	MeCN Et_3N
36	H	 · HCl Cis (−)	C–F	Pale yellow solid	231 ~ 234	[DMSO-d_6] δ ; 1.04(d, J=6.8Hz, 3H), 2.4-2.6(m, 1H), 3.5-4.1(m, 4H), 7.85((d, J=13.7Hz, 1H), 8.0-8.75(br, 3H), 8.90(s, 1H), 9.22(s, 1H)	〃

Table 10

Compound No.	基 R²	基 Y	基 Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
37	H	 · HCl	CIF	Pale yellow solid	268 ~ 275 decomposed	[DMSO-d_6] δ ; 3.15(brs, 4H), 3.46(brs, 4H), 8.00(d, J=11.7Hz, 1H), 8.98(s, 1H), 9.23(s, 1H), 9.43(brs, 1H), 9.73(brs, 1H)	MeCN Et$_3$N
38	H	· HCl	CIF	Pale yellow solid	244 ~ 250 decomposed	[DMSO-d_6] δ ; 2.77(s, 3H), 3.53(s, 4H), 7.98(d, J=11.7Hz, 1H), 8.98(s, 1H), 9.23(s, 1H), 11.0-11.3(br, 1H)	〃
39	H	· HCl	CIF	Pale yellow solid	Colored from 200℃, decomposed	[DMSO-d_6] δ ; 3.8-4.0(m, 2H), 7.90(d, J=12.7Hz, 1H), 8.38(brs, 3H), 8.92(s, 1H), 9.22(s, 1H),	〃

Example 17

Ethyl 2-(2,4,5-trifluorobenzoyl)-3-(1,2,5-thiadiazol-3-ylamino)acrylate (Compound No.40):

A mixture of ethyl 2,4,5-trifluorobenzoylacetate(8.94g), ethyl orthoformate(8.09g) and acetic anhydride-(16.7g) was stirred at 130 °C for 3 hours. After the solvent was removed in vacuo, a solution of 3-amino-1,2,5-thiadiazole hydrochloride (5.0g) and triethylamine (3.68g) in benzene(50ml) was added to the residue. The mixture was stirred at room temperature for 1 night. The solvent was evaporated and the residue was purified by chromatography on silicagel(chloroform as an eluent). The title compound No. 40 was obtained as a colorless solid (10.4g).

Melting point: 117-118 °C

^{1}H-NMR($CDCl_3$) δ; 1.04 and 1.19 (t,J = 7Hz,3H), 4.09-4.26(m,2H), 6.88-7.01(m,1H), 7.31-7.42 and 7.47-7.61(m,1H), 8.28 and 8.33(s,1H) 8.68 and 8.91(d,J = 12.5Hz,1H)

Example 18

Ethyl 6,7-difluoro-1-(1,2,5-thiadiazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.41):

To a solution of compound No.40 (1.6g) in tetrahydrofuran (50ml), 0.22g of sodium hydride (60% in oil) was added at room temperature for 1 hour. After addition of 5% aqueous citric acid solution, tetrahydrofuran was removed in vacuo. The aqueous solution was extracted with chloroform (50ml). Evaporation was carried out after drying over Na_2SO_4). The residue was purified by chromatography on silicagel (chloroform as an eluent). The title compound No. 41 was obtained as a colorless solid (1.13g).

Melting point: 189-192 °C

^{1}H-NMR(DMSO-d_6) δ;

1.28(t,J = 7Hz,3H), 4.25(q,J = 7Hz,2H), 7.69(dd,J = 6.5Hz,J = 12Hz,1H), 8.14(dd,J = 10.3Hz,J = 8.8Hz,1H), 8.81(s,1H),9.25(s,1H)

Example 19

6,7-Difluoro-1-(1,2,5-thiadiazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.42):

Compound No.41 (6.9g) was dissolved in acetic acid (100ml) and c-HCl (25ml). The solution was stirred at 100 °C for 1 hour. After evaporation of the solvent, 50ml of chloroform was added. The precipitate was filtrated and washed with diethylether (30ml). The title compound No. 42 was obtained as a colorless solid (6.0g).

Melting point: 255-256.5 °C

^{1}H-NMR(DMSO-d_6) δ;

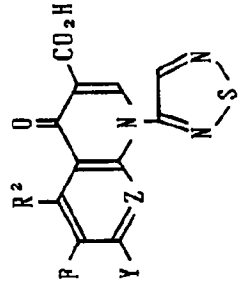
7.86(dd,J = 11.7Hz,J = 6.8Hz,1H), 8.36(dd,J = 10.2Hz,J = 8.8Hz,1H), 9.15(s,1H), 9.26(s,1H)

Example 20

Compound No.43 listed in Table 11 was synthesized in a similar manner to Example 4, proceeding from the corresponding compound No. 42 obtained in Example 19. The data are also shown in Table 11.

Table 11

Compound:



Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
43	H	(S) HO 	CH	Yellow solid	276 ~ 280	[DMSO-d₆] δ: 1.8-2.05(m,2H), 3.4-3.7(m,3H), 4.35(s,1H), 5.05(s,1H), 6.30(d,J=7.8Hz,1H), 7.86(d,J=14.2Hz,1H), 8.90(s,1H), 9.33(s,1H)	MeCN Et₃N

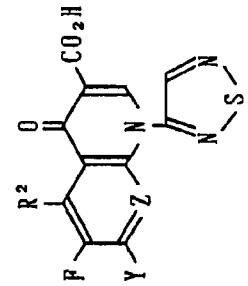
Example 21

Compounds Nos. 44-53 listed in Tables 12-14 were synthesized in a similar manner to Example 11, proceeding from the corresponding compound No.42 obtained in Example 19. The data are also shown in

Tables 12-14.

Table 12

Compound:



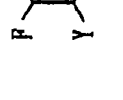
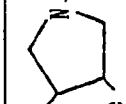
Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
44	H	(S) H_2N  · HCl	Cl H	Yellow needles	Colored from 235, 258.5-260	[DMSO-d_6] δ; 2.13(brs,1H), 2.20-2.41(m,1H), 6.34(d,J=7.3Hz,1H), 7.91(d,J=14.2Hz,1H), 8.48(brs,3H), 8.94(s,1H), 9.34(s,1H)	MeCN Et_3N
45	H	H_2N  Me Cis(−)·HCl	Cl H	Yellow needles	Colored from 210, 256-260	[DMSO-d_6] δ; 1.08(d,J=6.8Hz,3H), 2.60(brs,1H), 6.30(d,J=7.3Hz,1H), 7.92(d,J=14.2Hz,1H), 8.36(brs,3H), 8.94(s,1H), 9.34(s,1H)	〃

Table 1 3

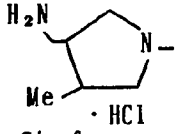
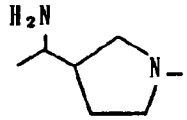
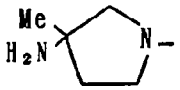
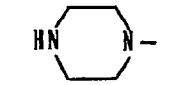
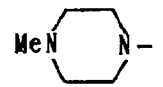
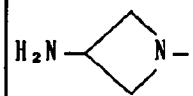
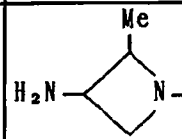
Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
46	H	 · HCl Cis form	C–H	Orange solid	190 ~ 197	[DMSO-d_6] δ ; 0.95(brs, 3H), 2.91(brs, 2H), 6.32(brs, 1H), 7.88(d, J=13.2Hz, 1H), 7.80~8.75(br, 3H), 8.91(s, 1H), 9.36(s, 1H)	MeCN Et_3N
47	H	 (3R, 1'S) · HCl	C–H	Pale red solid	280 ~ 285 Colored	[DMSO-d_6] δ ; 1.24(brs, 3H), 1.71(brs, 1H), 2.08(brs, 1H), 2.40(brs, 1H), 6.32(brs, 1H), 7.88(d, J=14.2Hz, 1H), 8.90(s, 1H), 9.32(s, 1H)	〃
48	H	 · HCl	C–H	Pale yellow solid	273 ~ 280	[DMSO-d_6] δ ; 1.45(s, 3H), 2.08(brs, 1H), 2.22(brs, 1H), 6.36(brs, 1H), 7.93(d, J=14.2Hz, 1H), 8.55(brs, 3H), 8.94(s, 1H) 9.35(s, 1H)	〃
49	H	 · HCl	C–H	Pale yellow solid	Colored from 250, decomposed in 264-266	[DMSO-d_6] δ ; 3.34(s, 4H), 6.98(d, J=6.8Hz, 1H), 8.03(d, J=13.2Hz, 1H), 9.02(s, 1H), 9.35(s, 1H), 9.30~9.82(br, 2H)	〃

Table 14

Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
50	H	 · HCl	CH	Pale yellow solid	Colored from 250, decomposed in 264-268	[DMSO-d_6] δ ; 2.80(s,3H), 3.7(brs,2H), 7.01(d,J=6.8Hz,1H), 8.05(d,J=13.2Hz,1H), 9.02(s,1H), 9.35(s,1H), 11.0～11.4(br,1H)	MeCN Et_3N
51	H	 · HCl	CH	Pale orange solid	230 ～ 245 decomposed	[DMSO-d_6] δ ; 3.85(brs,2H), 4.1～4.5(m,2H), 6.52(d,J=6.8Hz,1H), 7.94(d,J=11.7Hz,1H), 8.48(brs,3H), 8.93(s,1H), 9.33(s,1H)	〃
52	H	 · HCl	CH	Pale orange solid	Colored from 210, 220-228	[DMSO-d_6] δ ; 1.24(d,J=6.4Hz)と1.39(d,J=5.8Hz)合して3H, 3.5-4.1(m,2H), 4.44(brs,1H), 6.36(d,J=7.3Hz,1H), 7.96(d,J=12.7HZ), 8.59(brs,3H), 8.98(s,1H), 9.32(s,1H)	〃
53	H	· HCl  (1R,4R)	CH	Yellow solid	Colored from 280, decomposed	[DMSO-d_6] δ ; 1.9-2.15(m,2H), 3.6-3.8(m,3H), 4.44(s,1H), 4.80(s,1H), 6.54(d,J=7.3Hz,1H), 7.97(d,J=13.7Hz,1H), 8.95(s,1H), 9.15(brs,1H), 9.32(s,1H), 9.6(brs,1H)	〃

Example 22

Ethyl 3-(1,2,3-thiadiazol-4-yl-amino)-2-(2,6-dichloro-5-fluoronicotinoyl)acrylate (Compound No.54):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (5.6g), ethyl orthoformate (5.2ml) and acetic anhydride (5.6ml) was stirred at 130 °C for 3 hours. After the solvent was removed in vacuo, a solution of 4-amino-1,2,3-thiadiazole hydrochloride (2.75g) and triethylamine (2g) in chloroform (20ml) was added to the residue. The mixture was stirred at room temperature for 3 hours. The solvent was removed in vacuo. The residue was purified by chromatography on silicagel (chloroform/ethyl acetate 20:1 as an eluent). The title compound No. 54 was obtained as a pale yellow solid (7.8g).

Melting point: 110.5-113.5 °C

^{1}H-NMR($CDCl_3$) δ;

0.97 and 1.17 (t,J = 7Hz,3H),

4.0-4.25 (m,2H),

7.44 and 7.54 (d,J = 7Hz, 1H),

8.14 and 8.19 (s,1H),

9.0 and 9.22 (d,J = 13Hz,1H)

Example 23

Ethyl 7-chloro-6-fluoro-1-(1,2,3-thiadiazol-4-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.55):

To a solution of compound No.54 (7.8g) obtained in Example 22 in tetrahydrofuran (200ml), 0.8g of sodium hydride (60% in oil) was added at room temperature. The solution was stirred for 0.5 hour at the same temperature. After addition of aqueous 5% citric acid solution (40ml), tetrahydrofuran was removed in vacuo. The precipitate was filtrated and washed with water, ethanol and isopropyl ether. The title compound No. 55 was obtained as a pale yellow solid (6.1g).

Melting point: 188-192 °C

^{1}H-NMR($CDCl_3$) δ;

1.42(t,J = 7Hz,3H), 4.42(q,J = 7Hz,2H), 8.55(d,J = 11.8Hz,1H), 9.26(s,1H), 9.43(s,1H)

Example 24

7-Chloro-6-fluoro-1-(1,2,3-thiadiazol-4-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.56):

Compound No.55 (1g) obtained in Example 23 was dissolved in a mixture of acetic acid (10ml) and 6N-HCl (4ml). The solution was stirred at 100 °C for 0.5 hour. After cooling, the precipitate was filtrated and washed with water, ethanol and ether. The title compound No. 56 was obtained as a pale yellow solid (0.9g).

Melting point: 219-223 °C

^{1}H-NMR(DMSO-d_6) δ;

8.79(d,J = 7.3Hz,1H), 9.30(s,1H), 9.63(s,1H)

Example 25

6-Fluoro-7-(pyrrolidin-1-yl)-1-(1,2,3-thiadiazole-4-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.57):

A mixture of compound No.55 (216mg) obtained in Example 23 and pyrrolidine (100mg) in chloroform (5ml) was stirred at room temperature for 1 hour. After evaporation of the solvent, acetic acid (1ml) and 6N-HCl(1ml) were added to the residue, then stirred at 100 °C for 12 hours. After evaporation in vacuo, ethanol (5ml) was added for filtration, followed by washing with ethanol, chroloform and ether, successively. The title compound No. 57 was obtained as a colorless solid (140mg).

Melting point: Colored and decomposed at 273 °C or more.

^{1}H-NMR(DMSO-d_6) δ;

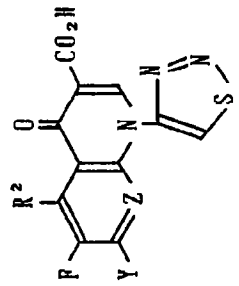
1.87(brs,4H), 3.2-3.9(br,4H), 8.04(d,J = 12.7Hz,1H), 9.09(s,1H), 9.65(s,1H)

Example 26

Compounds Nos. 58-62 listed in Tables 15 and 16 were synthesized in a similar manner to Example 25. The data are also shown in Tables 15-16.

Table 15

Compound:



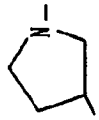
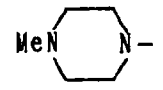
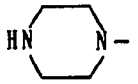
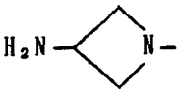
Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
58	H	 (S) · HCl	N	Yellow solid	Colored from 212, decomposed	[DMSO-d_6] δ ; 1.95~2.3(m,2H), 3.85(brs,2H), 8.15(d,J=12.2Hz,1H), 8.36(brs,3H), 9.11(s,1H), 9.70(s,1H)	$Et_3N/CHCl_3$ → AcOH, 6N-HCl
59	H	Cis(−)·HCl	N	Pale yellow solid	Colored from 246, 300 or more	[DMSO-d_6] δ ; 1.06(d,J=6.4Hz,3H), 2.4-2.7(br,1H), 3.1-4.2(m,5H), 8.14(d,J=12.2Hz,1H), 8.35(brs,3H), 9.11(s,1H), 9.72(s,1H),	〃

Table 16

Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
60	H	 · HCl	N	Pale yellow solid	Colored from 288, decomposed	[DMSO-d_6] δ ; 2.74(s, 3H), 2.9-3.2(m, 2H), 4.1-4.3(m, 2H), 8.32(d, J=13.2Hz, 1H), 9.17(s, 1H), 9.67(s, 1H), 10.4-10.6(br. 1H)	$Et_3N/CHCl_3$ ↓ ACOH, 6N-HCl
61	H	 · HCl	N	Pale yellow solid	Colored from 239, decomposed	[DMSO-d_6] δ ; 3.13(s, 4H), 3.80(s, 4H), 8.26(d, J=12.7Hz, 1H), 9.14(s, 1H), 9.50(brs, 2H), 9.67(s, 1H)	〃
62	H	 · HCl	N	Colorless solid	Colored from 240, decomposed	[DMSO-d_6] δ ; 3.51(brs, 3H), 3.73(brs, 2H), 8.15(d, J=10.2Hz, 1H), 8.42(brs, 2H), 8.56(brs, 1H), 9.1(s, 1H), 9.75(s, 1H)	〃

Example 27

Ethyl 2-(2,4,5-trifluorobenzoyl)-3-(1,2,3-thiadiazol-4-ylamino)acrylate (Compound No.63):

A mixture of ethyl 2,4,5-trifluorobenzoylacetate (4.92g), ethyl orthoformate (5.2ml) and acetic anhydride (5.6ml) was stirred at 130 °C for 8 hours. After the solvent was removed in vacuo, a solution of 4-amino-1,2,3-thiadiazole hydrochloride (2.75g) and triethylamine(2g) in chloroform(20ml) was added to the residue. The mixture was stirred at room temperature for 1 day. The solvent was removed in vacuo. The residue was purified by chromatography on silicagel (chloroform/ethyl acetate 30:1 as an eluent). The title compound No. 63 was obtained as a pale yellow solid (7.1g).

Melting point: 104-106 °C

^{1}H-NMR($CDCl_3$) δ;

1.04 and 1.18(t,J = 7Hz,3H), 4.05-4.2(m,2H), 6.85-7.0(m,1H), 7.2-7.6(m,1H), 8.02 and 8.09(s,1H) 8.73 and 9.06(d,J = 13Hz,1H),

Example 28

Ethyl 6,7-difluoro-1-(1,2,3-thiadiazol-4-yl)1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.64):

To a solution of compound No.63 (7.1g) obtained in Example 27 in tetrahydrofuran (200ml), 0.8g of sodium hydride (60% in oil) was added. Then the solution was stirred for 1 hour at room temperature. After addition of 5% aqueous citric acid solution (30ml), tetrahydrofuran was removed in vacuo. The aqueous solution was extracted with chloroform (300ml). The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silicagel (chloroform/ethyl acetate 5:1 as an eluent). The title compound No. 64 was obtained as a yellow solid (3.3g).

Melting point: 198-203 °C

^{1}H-NMR($CDCl_3$) δ;

1.34(t,J = 7Hz,3H), 4.29(q,J = 7Hz,2H), 6.81(dd,J = 5.9Hz,J = 10.7Hz,1H), 8.08(dd,J = 8.3Hz,J = 10.2Hz,1H), 8.46(s,1H), 9.43(s,1H)

Example 29

6,7-Difluoro-1-(1,2,3-thiadiazol-4-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.65):

Compound No.64 (0.18g) obtained in Example 28 was dissolved in acetic acid (1ml) and 6N-HCl (1ml). The solution was stirred at 100 °C for 1 hour. Water (30ml) was added thereto, and the solid matter was collected by filtration, followed by washing with water, ethanol and ether successively. The title compound No. 65 was obtained as a yellow solid (115mg).

Melting point: 239-244 °C

^{1}H-NMR(DMSO-d_6) δ;7.54(dd,J = 11.7Hz,J = 6.8Hz,1H), 8.36(dd,J = 9.8Hz,J = 8.8Hz,1H), 9.10(s,1H), 9.77-(s,1H)

Example 30

Ethyl 7-chloro-6-fluoro-1-(3-methyl-1,2,4-thiadiazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.66):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (4.2g), ethyl orthoformate (3.9ml) and acetic anhydride (4.3ml) was stirred at 135 °C for 2 hours. After the solvent was removed in vacuo, the residue was added with chloroform (20ml) and ethanol (10ml). 3-Methyl-5-amino-1,2,4-thiadiazole (1.73g) was added thereto at room temperature and allowed to react at the same temperature for 1 hour. The solvent was removed. The residue was purified by chromatography on silicagel (chloroform/methanol 40:1 as an eluent). An yellow oil (5.8g) was obtained. To a solution of this oily compound (400g) in N,N-dimethylformamide (5ml), 40mg of sodium hydride (60% in oil) was added. Then the solution was stirred for 0.5 hour at 100 °C. The solvent was removed. The residue was added with chloroform and water for separating an organic phase. The organic phase was washed dried (Na_2SO_4) and evaporated for collecting the precipitated solid. The title compound N0.66 was obtained as a colorless solid (0.18g).

Melting point: 235-237 °C

^{1}H-NMR($CDCl_3$) δ;
1.46(t,J = 7Hz,3H), 2.69(s,3H), 4.47(q,J = 7Hz,2H), 8.54(d,J = 7Hz,1H), 9.96(s,1H)

Example 31

7-Chloro-6-fluoro-1-(3-methyl-1,2,4-thiadiazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.67):

Compound No.66 (1g) obtained in Example 30 was dissolved in acetic acid (40ml) and c-HCl (10ml). The solution was stirred at 100 °C for 0.5 hour. After evaporating the solvent, the residue was added with water followed by filtration, washing with water, ethanol, ether and n-hexane successively. The title compound No. 67 was obtained as a colorless solid (0.84g).

Melting point: 260-262 °C
^{1}H-NMR(DMSO-d_6) δ;
2.63(s,3H), 8.78(d,J = 8Hz,1H), 9.75(s,1H)

Example 32

6-Fluoro-7-(pyrrolidin-1-yl)-1-(3-methyl-1,2,4-thiadiazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.68):

Compound No.66 (100mg) obtained in Example 30 was dissolved in chloroform (4ml), to which pyrrolidine (44mg) and triethylamine (30mg) were added for allowing to react at room temperature for 10 minutes. After evaporation of the solvent, acetic acid (2ml) and c-HCl (1ml) were added, then stirred at 100 °C for 1.5 hours. The precipitated solid was collected by filtration and washed with ethanol, ether and n-hexane, successively. The title compound No. 68 was obtained as a pale yellow solid (40mg).

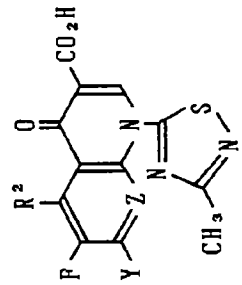
Melting point: 300 °C or more
^{1}H-NMR($CDCl_3$) δ;
2.15(brs,4H), 2.66(s,3H), 3.98(s,4H), 8.01(d,J = 13Hz,1H), 10.02(s,1H)

Example 33

Compounds Nos. 69-72 listed in Tables 17 -18 were synthesized in a similar manner to Example 32. The data are also shown in Tables 17-18.

Table 17

Compound:



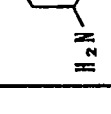
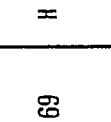
Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
69	H	· HCl  S体	N	Pale yellow solid	Colored from 220, decomposed	[DMSO-d_6] δ ; 2.26(brs, 1H), 2.40(brs, 1H), 2.64(s, 3H), 4.07-4.25(br, 4H), 8.19(d, J=13Hz, 1H), 8.0-8.7(br, 3H), 9.73(s, 1H)	MeCN Et_3N → Hydrochloric acid
70	H	 · HCl	N	Colorless solid	Colored from 250, decomposed	[DMSO-d_6] δ ; 2.65(s, 3H), 2.84(s, 3H), 8.35(d, J=13Hz, 1H), 9.75(s, 1H), 11.0-11.5(br, 1H)	〃

Table 18

Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
71	H	· HCl	N	Yellow solid	Colored from 260, decomposed	[DMSO-d_6] δ : 2.65(s, 3H), 4.09(brs, 4H), 8.33(d, J=13Hz, 1H), 9.75(s, 1H)	MeCN → Et_3N → Hydrochloric acid
72	H	· HCl Cis (−)	N	Pale yellow solid	Colored from 190, decomposed	[DMSO-d_6] δ : 1.16(d, J=7Hz, 3H), 2.64(s, 3H), 2.80(brs, 1H), 3.74-4.04(br, 2H), 8.18(d, J=13Hz, 1H), 9.72(s, 1H)	MeCN → Et_3N → Hydrochloric acid

Example 34

Ethyl 6,7-difluoro-1-(3-methyl-1,2,4-thiadiazol-5-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.73):

A mixture of ethyl 2,4,5-trifluorobenzoylacetate (3.7g), ethyl orthoformate (3.9ml) and acetic anhydride (4.3ml) was stirred at 135 °C for 3 hours. After the solvent was removed in vacuo, the residue was added with chloroform (20ml) and ethabol (10ml). 3-Methyl-5-amino-1,2,4-thiadiazole (1.73g) was added thereto for allowing to react for 15 hours at the same temperature. The solvent was removed. The residue was purified by chromatography on silicagel(chloroform/ethyl acetate 1:1 as an eluent). An yellow oil (4.9g) was obtained. To a solution of this oily compound (4.5g) in N,N-dimethylformamide (60ml), 490mg of sodium hydride (60% in oil) was added . Then the solution was stirred for 5 minutes at 100 °C. The solvent was removed. The residue was added with chloroform and water, for extracting an organic layer, followed by evaporation. The precipitated solid was collected and washed with ethanol, ether and n-hexane, successively. The title compound No. 73 was obtained as a pale brown solid (2.4g).

Melting point: 157-159 °C

^{1}H-NMR($CDCl_3$) δ;

1.42(t,J = 7Hz,3H), 2.78(s,3H), 4.43(q,J = 7Hz,2H), 8.17-8.32(m,2H), 8.77(s,1H)

Example 35

6,7-Difluoro-1-(3-methyl-1,2,4-thiadiazol-5-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.74):

Compound No.73 (1.2g) obtained in Example 34 was dissolved in a mixture of tetrahydrofuran (40ml) and HCl (10ml). The solution was reacted at 100 °C for 40 minutes. After evaporation, to the residue was added water, and the solid matter was collected by filtration, followed by washing with water, ethanol, ether and n-hexane, successively. The title compound No. 74 was obtained as a pale brown solid (0.9g).

Melting point: 235-238 °C

^{1}H-NMR(DMSO-d_6) δ;

2.69(s,3H), 8.06(dd,J = 7Hz,J = 12Hz,1H), 8.32(dd,J = 9HZ,J = 10Hz,1H), 9.04(s,1H)

Example 36

6-Fluoro-7-(3-aminoazetidin-1-yl)-1-(3-methyl-1,2,4-thiadiazol-5-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylicacid hydrochloride (Compound No. 75):

Compound No.74 (90mg) obtained in Example 35 was added to acetonitrile (4ml), to which triethylamine (0.12g) and 3-aminoazetidine dihydrochloride (54mg) were further added for allowing to react at 80 °C for 60 minutes. After cooling, the precipitate was filtrated and washed with ethanol, ether and n-hexane, successively to obtain a pale yellow solid (43mg). A 20mg portion was taken and added to a mixture of tetrahydrofuran (2ml) and 6N-HCl (0.5ml), and stirred for 5 minutes. The precipitate was collected by filtration and washed with water, ethanol, ether and n-hexane successively. The title compound No. 75 was obtained as a pale yellow solid (15mg).

Melting point: Colored and decomposed at 270 °C or more.

^{1}H-NMR(DMSO-d_6) δ;

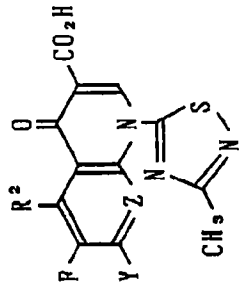
2.69(s,3H), 4.16(br,3H), 4.42(brs,2H), 6.67(d,J = 8Hz,1H), 7.92(d,J = 13Hz,1H), 8.5-8.7(brs,3H), 8.89(s,1H)

Example 37

Compound No.76 listed in Table 19 was prepared in a similar manner to Example 36. The data are also shown in Table 19.

Table 19

Compound:



Compound No.	Group			Property	Melting point (℃)	^{1}H-NMR	Solvent
	R^2	Y	Z				
76	H	· HCl Cis (−)	C—H	Pale yellow solid	Colored from 159, decomposed	[DMSO-d_6] δ: 1.09(brs, 3H), 2.51-2.71(m, 1H), 2.71(s, 3H), 3.08-3.90(m, 5H), 6.72(d, J=7Hz, 1H), 7.92(d, J=14Hz, 1H), 8.2-8.6(br, 3H) 8.92(s, 1H)	MeCN Et_3N → Hydro-chloric acid

Example 38

Ethyl 3-(4-methyl-1,2,5-oxadiazol-3-ylamino)-2-(2,6-dichloro-5-fluoronicotinoyl)acrylate (Compound No.77):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (1.4g), ethyl orthoformate (1.3ml) and acetic anhydride (1.4ml) was stirred at 130 °C for 17 hours. After the solvent was removed in vacuo, a solution of 3-amino-4-methyl-1,2,5-oxadiazole (545mg) in chloroform (5ml) was added to the residue. The mixture was stirred at room temperature for 24 hours. The solvent was removed and the residue was purified by chromatography on silicagel(chloroform as an eluent). The title compound No. 77 was obtained as a colorless solid (770mg).

Melting point: 139-141.5 °C

^{1}H-NMR($CDCl_3$) δ;

0.97 and 1.18(t,J = 7Hz,3H), 2.47 and 2.51(s,3H), 4.05-4.3(m,2H), 7.3 and 7.43(d,J = 6.8Hz,1H), 8.72 and 8.82(d,J = 12.4Hz,1H)

Example 39

Ethyl 7-chloro-6-fluoro-1-(4-methyl-1,2,5-oxadiazol-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.78):

To a solution of compound No.77 (0.7g) obtained in Example 38 in tetrahydrofuran (30ml), 0.074g of sodium hydride (60% in oil) was added with ice cooling. Then the solution was stirred for 4 hours at room temperature. The solvent was removed. After addition of aqueous 5% citric acid solution (20ml), extraction was carried out with chloroform (50ml). The chloroform was evaporated and the residue was purified by chromatography on silicagel (chloroform/ethyl acetate 1:1 as an eluent). The title compound No. 78 was obtained as a pale yellow solid (0.41g).

Melting point: 211-216 °C

^{1}H-NMR($CDCl_3$) δ;

1.40(t,J = 7Hz,3H), 2.41(s,3H), 4.41(q,J = 7Hz,2H), 8.49(d,J = 7.8Hz,1H), 8.66(s,1H)

Example 40

7-Chloro-6-fluoro-1-(4-methyl-1,2,5-oxadiazol-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.79):

Compound No.78 (30mg) obtained in Example 39 was dissolved in acetic acid (2ml) and 6N-HCl (0.5ml). The solution was stirred at 100 °C for 0.5 hour. After cooling and addition of water (10ml), the precipitate was filtrated and washed with ethanol and ether. The title compound No. 79 was obtained as a colorless solid (5mg).

Melting point: 242-247 °C

^{1}H-NMR(DMSO-d_6) δ;

2.33(s,3H), 8.77(d,J = 8Hz,1H), 9.09(s,1H)

Example 41

6-Fluoro-7-(4-methylpiperazin-1-yl)-1-(4-methyl-1,2,5-oxadiazol-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrochloride (Compound No.80):

A mixture of compound No.78 (0.15g)obtained in Example 40, triethylamine (40mg) and N-methylpiperazine (70mg) in acetonitrile (5ml) was stirred at 50 °C for 20 minutes. After the solvent was removed, 1ml of 6N-HCl and 1ml of acetic acid were added, then stirred at 100 °C for 1 hour. After the solvent was removed in vacuo, ethanol(5ml) was added to the residue. The precipitate was collected by filtration and washed with ethanol and ether. The title compound No. 80 was obtained as a colorless solid (0.16g).

Melting point: 254-258 °C

^{1}H-NMR(DMSO-d_6) δ;

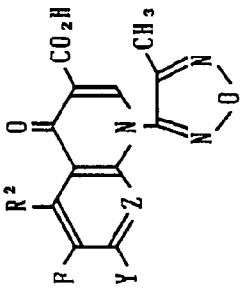
2.31(s,3H), 2.74(s,3H), 3.08(brs,2H), 3.3-3.6(m,4H), 4.18(brs,2H), 8.29(d,J = 13.2Hz,1H), 9.00(s,1H)

Example 42

Compounds Nos. 81-89 listed in Tables 20-22 were synthesized in a similar manner to Example 41. The data are also shown in Tables 20-22.

Table 20

Compound:



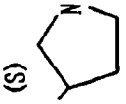
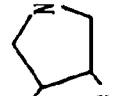
Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
81	H	(S) H_2N  · HCl	N	Pale yellow solid	Colored from 245, decomposed from 272	[DMSO-d_6] δ : 2.0-2.4(m, 2H), 2.34(s, 3H), 3.2-4.1(m, 5H), 8.13(d, J=12Hz, 1H), 8.37(brs, 3H), 8.92(s, 1H)	Et_3N/CH_3CN → AcOH, 6N-HCl
82	H	H_2N  Me Cis (−) · HCl	N	Pale yellow solid	Colored from 255, decomposed from 294	[DMSO-d_6] δ : 1.08(d, J=6.8Hz, 3H), 2.34(s, 3H), 2.4-2.7(br, 1H), 3.4-4.2(m, 3H), 8.14(d, J=12.2Hz, 1H), 8.37(brs, 3H), 8.92(s, 1H)	〃

Table 21

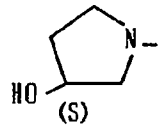
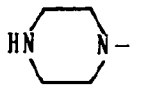
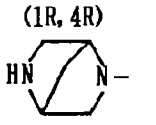
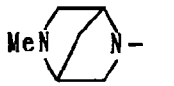
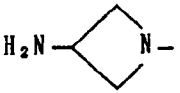
Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
83	H	 · HCl	N	Colorless solid	300 or more	[DMSO-d_6] δ ; 1.44(s, 3H), 1.9-2.4(m, 2H), 2.34(s, 3H), 3.4-4.3(m, 4H), 8.13(d, J=14.7Hz, 1H), 8.56(brs, 3H), 8.92(s, 1H)	Et_3N/CH_3CN ↓ AcOH, 6N-HCl
84	H		N	Colorless solid	224 ~ 226.5	[DMSO-d_6] δ ; 1.9(brs, 2H), 2.31(s, 3H), 3.9(brs, 1H), 4.3(brs, 1H), 5.05(brs, 1H), 8.06(d, J=12.2Hz, 1H), 8.91(s, 1H)	〃
85	H	 · HCl	N	Pale yellow solid	Decomposed from 276	[DMSO-d_6] δ ; 2.32(s, 3H), 3.18(s, 4H), 3.81(s, 4H), 8.24(d, J=13.2Hz, 1H), 8.98(s, 1H), 9.59(brs, 1H), 9.79(brs, 1H)	〃
86	H	 · HCl	N	Colorless solid	Decomposed from 292	[DMSO-d_6] δ ; 1.9-2.2(m, 2H), 2.32(s, 3H), 4.45(s, 1H), 8.21(d, J=13Hz, 1H), 8.96(s, 1H), 8.95(brs, 2H)	〃

Table 22

Compound No.	Group			Property	Melting point (℃)	^{1}H-NMR	Solvent
	R^2	Y	Z				
87	H	(1R, 4R)  · HCl	N	Colorless solid	Decomposed from 297	[DMSO-d_6] δ ; 2.1-2.4(m, 2H), 2.33(s, 3H), 2.83(s, 3H), 3.0-3.2(m, 1H) 3.5-3.7(m, 1H), 4.38(s, 1H), 8.22(d, J=11.7Hz, 1H), 8.96(s, 1H), 10.4(brs, 1H)	Et_3N/CH_3CN ↓ AcOH, 6N-HCl
88	H	 · HCl	N	Colorless solid	Decomposed from 241	[DMSO-d_6] δ ; 2.31(s, 3H), 3.57(brs, 2H), 3.72(brs, 2H), 8.14(d, J=10.2Hz, 1H), 8.44(brs, 2H), 8.65(brs, 1H), 8.93(s, 1H)	〃
89	H	 · HCl	N	Colorless solid	218 ~ 225	[DMSO-d_6] δ ; 2.33(s, 3H), 2.85(brs, 2H), 3.18(brs, 2H), 8.12(brs, 3H), 8.47(d, J=8.8Hz, 1H), 9.18(s, 1H)	〃

Example 43

Ethyl 3-(4-methyl-1,2,5-oxadiazol-3-ylamino)-2-(2,4,5-trifluorobenzoyl)acrylate (Compound No.90):

A mixture of ethyl 2,4,5-trifluorobenzoylacetate (2.46g), ethyl orthoformate (2.6ml) and acetic anhydride (2.8ml) was stirred at 130 °C for 6 hours. After the solvent was removed in vacuo, a solution of 3-amino-4-methyl-1,2,5-oxadiazole (1.04g) in chloroform (10ml) was added to the residue. The mixture was stirred at room temperature for 24 hours, then the solvent was removed. The residue was purified by chromatography on silicagel (chloroform as an eluent). The title compound No. 90 was obtained as a colorless solid (1.95g).

Melting point: 104-107 °C

^{1}H-NMR($CDCl_3$) δ;

1.05 and 1.20(t,J = 7Hz,3H), 2.45 and 2.48(s,3H), 4.1-4.3(m,2H), 6.85-7.0(m,1H), 7.3-7.41 and 7.48-7.6-(m,1H), 8.39 and 8.69(q,J = 12Hz,1H)

Example 44

Ethyl 6,7-difluoro-1-(4-methyl-1,2,5-oxadiazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.91):

To a solution of compound No.90 (1.9g) obtained in Example 43 in tetrahydrofuran (50ml), 216mg of sodium hydride (60% in oil) was added. Then the solution was stirred for 6 hour at the room temperature. The solvent was removed and the residue was added with aqueous 5% citric acid solution (30ml), followed by extraction with chloroform (50ml), and evaporation. The residue was purified by chromatography on silicagel (chloroform/ethyl acetate 1:1 as an eluent). The title compound No. 91 was obtained as a colorless solid (1.18g).

Melting point: 178-180.5 °C

^{1}H-NMR($CDCl_3$) δ;

1.40(t,J = 7Hz,3H), 2.41(s,3H), 4.39(q,J = 7Hz,2H), 6.81(dd,J = 10.2Hz,J = 5.8Hz,1H), 8.30-(dd,J = 9.8Hz,J = 8.8Hz,1H), 8.39(s,1H)

Example 45

6,7-Difluoro-1-(4-methyl-1,2,5-oxadiazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.92):

Compound No.91 (0.1g) obtained in Example 44 was dissolved in acetic acid (3ml) and 6N-HCl (1ml). The solution was stirred at 100 °C for 2 hours. After cooling, the precipitate was filtrated and washed with water, ethanol and ether. The title compound was obtained as colorless solid(60mg).

Melting point: 238-241 °C

^{1}H-NMR(DMSO-d_6) δ;

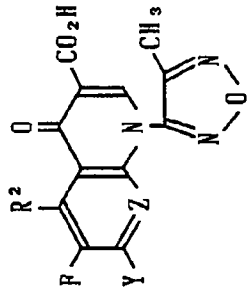
2.33(s,3H), 7.78(dd,J = 11.2Hz,J = 6.3Hz,1H), 8.34(dd,J = 10.3Hz,J = 8.3Hz,1H), 9.16(s,1H)

Example 46

Compound Nos. 93-95 listed in Tables 23 and 24 were synthesized in a similar manner to Example 11, proceeding from the corresponding compound No.92 obtained in Example 45. The data are also shown in Tables 23-24.

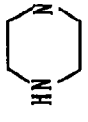
Table 23

Compound:



Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
93	H	(S) · HCl	CH	Pale yellow solid	Decomposed from 292	[DMSO-d_6] δ: 2.0-2.3(m, 2H), 2.36(s, 3H), 3.7-4.0(m, 2H), 5.98(d, J=6.8Hz, 1H), 7.93(d, J=14Hz, 1H), 8.37(brs, 3H), 8.97(s, 1H)	Et_3N/CH_3CN ↓ AcOH, 6N-HCl
94	H	· Cis (—) · HCl	CH	Pale yellow solid	274 ~ 279	[DMSO-d_6] δ: 1.08(d, J=6.8Hz, 3H), 2.36(s, 3H), 2.5-2.7(m, 1H), 3.5-4.0(m, 4H), 5.95(d, J=7.3Hz, 1H), 7.93(d, J=14Hz, 1H), 8.1-8.8(br, 3H) 8.97(s, 1H)	〃

Table 24

Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
95	H	 · HCl	CH	Colorless solid	278 ~ 285	[DMSO-d₆] δ: 2.34(s, 3H), 3.23(s, 4H), 3.44(s, 4H), 6.66(d, J=6.8Hz, 1H), 8.04(d, J=12.7Hz, 1H), 9.06(s, 1H), 9.52(brs, 2H)	Et₃N/CH₃CN → AcOH, 6N-HCl

Example 47

Ethyl 3-(1,2,4-triazol-4-ylamino)-2-(2,4,5-trifluorobenzoyl)acrylate (Compound No.96):

A mixture of ethyl 2,4,5-trifluorobenzoylacetate (4.29g), ethyl orthoformate (5.2ml) and acetic anhydride (5.6ml) was stirred at 130 °C for 6 hours. After the solvent was removed in vacuo, a solution of 4-amino-1,2,4-triazole (1.77g) and ethanol (5ml) in chloroform (30ml) was added to the residue. The mixture was stirred at room temperature for 6 hours. The solvent was removed, the residue was added with 100ml of hexane, then the solution was stirred for 1 hour. The precipitate was filtrated. The title compound No. 96 was obtained as a colorless solid (6.2g).

Melting point: 239-240 °C

^{1}H-NMR($CDCl_3$) δ;

1.0-1.2(m,3H), 4.14(q,J = 7Hz,2H), 6.85-7.1(m,1H), 7.3-7.6(m,1H), 8.18(brs,1H), 8.46(s,2H)

Example 48

Ethyl 6,7-difluoro-1-(1,2,4-triazol-4-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.97):

A solution of compound No.96 (6.2g) obtained in Example 47 and anhydrous potassium carbonate (2.5g) in N,N-dimethylformamide (20ml) was stirred for 4 hours at 90 °C. The solvent was removed in vacuo. After addition of water, the precipitate was filtrated and washed with water, ethanol and ether successively. The title compound No. 97 was obtained as a pale green solid (3.7g).

Melting point: 269-274 °C

^{1}H-NMR(DMSO-d_6) δ;

1.26((t,J = 7Hz,3H), 4.22(q,J = 7Hz,2H), 6.9(dd,J = 11Hz,J = 6.4Hz,1H), 8.14(dd,J = 10.2Hz,J = 8.3Hz,1H), 9.01(s,1H),9.20(s,2H)

Example 49

6,7-Difluoro-1-(1,2,4-triazol-4-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.98):

Compound No.97 (3.0g) obtained in Example 48 was dissolved in a mixture of tetrahydrofuran (120ml) and 6N-HCl (30ml). The solution was stirred at reflux temperature for 20 minutes. After cooling, 200ml of water was added. The precipitate was filtrated and washed with ethanol, ether and hexane. The title compound No. 98 was obtained as a colorless solid (1.6g).

Melting point: 270 °C decomposed

^{1}H-NMR(DMSO-d_6) δ;

7.09(dd,J = 11Hz,J = 6Hz,1H), 8.36(dd,J = 10Hz,J = 8Hz,1H), 9.18(s,2H), 9.34(s,1H)

Example 50

6-Fluoro-7-(4-methylpiperazin-1-yl)-1-(1,2,4-triazol-4-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.99):

A mixture of compound No.98 (50mg) obtained in Example 49 and N-methylpiperazine (40mg) in acetonitrile (3ml) was stirred at 80 °C for 60 minutes. After the solvent was removed, ethanol was added to the residue. The precipitate was filtrated and washed with ethanol and ether successively. The title compound No. 99 was obtained as a yellow solid (43mg).

Melting point: 270 °C decomposed

^{1}H-NMR(DMSO-d_6) δ;

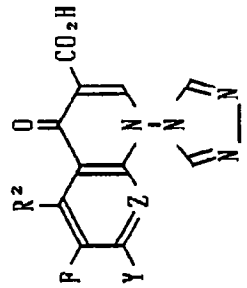
2.20(s,3H), 2.43(brs,4H), 3.13(brs,4H), 5.83(d,J = 7Hz,1H), 8.00(d,J = 14Hz,1H), 9.21(s,2H), 9.26(s,1H)

Example 51

Compound Nos. 100-103 listed in Tables 25 and 26 were synthesized in a similar manner to Example 50. The data are also shown in Tables 25 and 26.

Table 25

Compound:



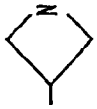
Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
100	H		CH	Pale yellow solid	300 or more	[DMSO-d₆] δ: 2.81(brs,4H), 3.05(brs,4H), 5.79(d,J=7Hz,1H), 7.98(d,J=14Hz,1H), 9.22(s,2H), 9.25(s,1H)	CH₃CN Et₃N
101	H		CH	Colorless solid	300 or more	[DMSO-d₆] δ: 4.21(brs,2H) 5.11(d,J=7Hz,1H), 7.87(d,J=13Hz,1H), 9.15(s,2H), 9.20(s,1H)	CH₃CN Et₃N

Table 26

Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	^{1}H-NMR	Solvetn
102	H	 S-form	CH	Brown solid	300 or more	[DMSO-d_6] δ : 1.59-2.01(m, 2H), 2.76-3.19(m, 5H), 5.27(d, J=7Hz, 1H), 7.86(d, J=14Hz, 1H), 9.09(s, 1H), 9.23(s, 2H)	CH_3CN
103	H	Cis (-)	CH	Pale yellow solid	300 or more	[DMSO-d_6] δ : 0.96(d, J=7Hz, 3H), 2.07-2.22(m, 1H), 3.17-3.52(m, 5H), 5.25(d, J=7Hz, 1H), 7.85(d, J=14Hz, 1H), 9.13(s, 1H), 9.22(s, 2H)	CH_3CN Et_3N

Example 52

Ethyl 3-(1,2,4-triazol-4-ylamino)-2-(2,6-dichloro-5-fluoronicotinoyl)acrylate (Compound No.104):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (4.2g), ethyl orthoformate (3.9ml) and acetic anhydride (4.3ml) was stirred at 130 °C for 2 hours. After the solvent was removed in vacuo, a solution of 4-amino-1,2,4-triazole (1.26g) in chloroform (20ml) was added to the residue. The mixture was stirred at room temperature for 4 hours. The solvent was removed and the residue was added with isopropylether. The precipitate was filtrated. The title compound No. 104 was obtained as a yellow solid (5.5g).

Melting point: 89-95 °C

^{1}H-NMR($CDCl_3$) δ;

1.27(t,J = 7Hz,3H), 4.24(q,J = 7Hz,2H), 8.6(d,J = 7.6Hz,1H), 9.04(s,2H), 9.22(s,1H)

Example 53

Ethyl 7-chloro-6-fluoro-1-(1,2,4-triazol-4-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.105):

A solution of compound No.104 (0.95g) obtained in Example 52 and sodium hydrogencarbonate (0.21g) in N,N-dimethylformamide (5ml) was stirred for 1 hour at 100 °C. The solution was removed in vacuo. After addition of water to the residue, the precipitate was filtrated and washed with water, ethanol and ether successively. The title compound No. 105 was obtained as a pale yellow solid (0.52g).

Melting point: 257 °C decomposed

^{1}H-NMR($CDCl_3$) δ;

1.08(t,J = 7Hz,3H), 4.11(q,J = 7Hz,2H), 7.47(d,J = 6.8Hz,1H), 8.27(s,1H), 8.47(s,2H)

Example 54

7-Chloro-6-fluoro-1-(1,2,4-triazol-4-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.106):

Compound No.105 (1.0g) obtained in Example 53 was dissolved in acetic acid (40ml) and 6N-HCl (10ml). The solution was stirred at 100 °C for 0.5 hour. After cooling, water (100ml) is added thereto, and the precipitate was filtrated and washed with ethanol and ether successively. The title compound No. 106 was obtained as a pale yellow solid (0.48g).

Melting point: 230 °C decomposed

^{1}H-NMR(DMSO-d_6) δ;

8.77(d,J = 8Hz,1H), 9.03(s,2H), 9.44(s,1H)

Example 55

6-Fluoro-7-(4-methylpiperazin-1-yl)-1-(1,2,4-triazol-4-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.107):

A mixture of compound No.106 (30mg) obtained in Example 54 and N-methylpiperazine (20mg) in acetonitrile (2ml) was stirred at 80 °C for 60 minutes. After the solvent was removed, ethanol (5ml) was added to the residue. The precipitate was filtrated and washed with ethanol and ether successively. The title compound No. 107 was obtained as a colorless solid (7mg).

Melting point: 271 °C decomposed

^{1}H-NMR(DMSO-d_6) δ;

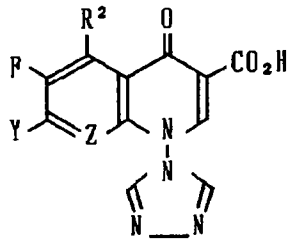
2.32(s,3H), 3.06(brs,4H), 3.59(brs,4H), 8.21(d,J = 13Hz,1H), 9.01(s,2H), 9.33(s,1H)

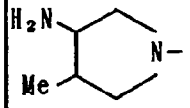
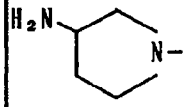
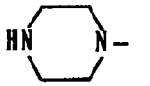
Example 56

Compound Nos. 108-110 listed in Table 27 were prepared in a similar manner to Example 55. The data are also shown in Table 27.

Table 2 7

Compound :



Compound No.	Group			Property	Melting point (℃)	^{1}H-NMR	Solvent
	R^a	Y	Z				
108	H	 Cis (−)	N	Colorless solid	Decomposed from 220	[DMSO-d_6] δ ; 0.96(brs, 3H), 2.11-2.32(m, 1H), 2.83-3.93(m, 5H), 8.04(d, J=13Hz, 1H), 9.00(s, 2H), 9.22(s, 1H)	CH_3CN Et_3N
109	H	 S 体	N	Pale brown solid	Decomposed from 238	[DMSO-d_6] δ ; 1.58-2.01(m, 2H), 2.73-3.95(m, 5H), 8.05(d, J=12Hz, 1H), 8.99(s, 2H), 9.23(s, 1H)	CH_3CN Et_3N
110	H		N	Pale brown solid	Decomposed from 240	[DMSO-d_6] δ ; 2.70(brs, 4H), 3.64(brs, 4H), 8.14(d, J=14Hz, 1H), 9.01(s, 2H), 9.29(s, 1H)	CH_3CN Et_3N

Example 57

Ethyl 3-(1,2,5-thiadiazol-3-yl-methylamino)-2-(2,6-dichloro-5-fluoronicotinoyl)acrylate (Compound No.111):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (0.56g), ethyl orthoformate (0.5ml) and acetic anhydride (0.57ml) was stirred at 130 °C for 3 hours. After the solvent was removed in vacuo, a solution of 3-aminomethyl-1,2,5-thiadiazole (0.24g) in benzene (5ml) and methanol (2ml) was added to the residue. The mixture was stirred at room temperature for 0.5 hour. The solvent was removed, the residue was added with isopropylether (10ml), and the precipitate was filtrated. The title compound No. 111 was obtained as a pale yellow solid (573mg).

Melting point: 108-110 °C

^{1}H-NMR($CDCl_3$) δ;

0.89 and 1.06(t,J = 7Hz, 3H), 3.9-4.15(m,2H), 4.97(d,J = 5.8Hz,2H), 7.37 and 7.43(d,J = 7Hz, 1H), 8.35 and 8.39(d,J = 14Hz,1H), 8.56 and 8.58(s, 1H)

Example 58

Ethyl 7-chloro-6-fluoro-1-(1,2,5-thiadiazol-3-ylmethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.112):

To a solution of compound No.111 (0.55g) obtained in Example 57 in tetrahydrofuran (20ml), 56mg of sodium hydride (60% in oil) was added. Then the solution was stirred for 0.5 hour at room temperature. The solvent was evaporated, an aqueous 5% citric acid solution (10ml) was added thereto, and extracted with chloroform (50ml). The extract was dried over Na_2SO_4, and the solvent was removed. Isopropylether (10ml) was added to the residue, and the precipitate was filtrated. The title compound No. 112 was obtained as a colorless solid (425mg).

Melting point: 175-177 °C

^{1}H-NMR($CDCl_3$) δ;

1.41(t,J = 7Hz,3H), 4.41(q,J = 7Hz,2H), 5.79(s,2H), 8.45(d,J = 7.3Hz,1H), 8.73(s,1H), 8.83(s,1H)

Example 59

7-Chloro-6-fluoro-1-(1,2,5-thiadiazol-3-ylmethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.113):

Compound No.112 (0.4g) obtained in Example 158 was dissolved in acetic acid (4.5ml) and 6N-HCl (1.5ml). The solution was stirred at 100 °C for 2 hours. After cooling, the precipitate was filtrated and washed with water, ethanol and ether. The title compound No. 113 was obtained as a pale yellow solid (0.33g).

Melting point: 231-232.5 °C

^{1}H-NMR(DMSO-d_6) δ;

6.13(s,2H), 8.72(d,J = 7.8Hz,1H), 8.93(s,1H), 9.47(s,1H)

Example 60

6-Fluoro-7-(piperazin-1-yl)-1-(1,2,5-thiadiazole-3-ylmethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.114):

A mixture of compound No.113 (70mg) obtained in Example 59, piperazine (26mg) triethylamine (60mg) in acetonitrile (2ml) was stirred at 80 °C for 90 minutes. After cooling, the precipitate was filtrated and washed with ethanol and ether successively. The title compound No. 114 was obtained as a pale orange solid (71mg).

Melting point: 219.5-223 °C

^{1}H-NMR(DMSO-d_6) δ;

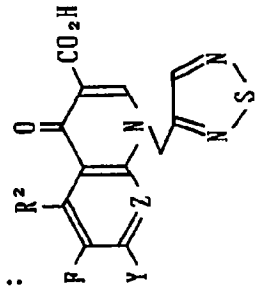
2.64(s,4H), 3.57(s,4H), 5.99(s,2H), 8.05(d,J = 14Hz,1H), 8.91(s,1H), 9.25(s,1H)

Example 61

Compounds Nos. 115-116 listed in Table 28 were prepared in a similar manner to Example 60. The data are also shown in Table 28.

Table 28

Compound:



Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
115	H	(S) H₂N	N	Pale yellow solid	208 ~ 213	[DMSO-d₆] δ ; 1.5-1.7(br, 1H), 1.7-2.1(br, 1H), 2.9-3.2(m, 2H), 5.98(s, 2H), 7.95(d, J=13.7Hz, 1H), 8.91(s, 1H), 9.18(s, 1H)	Et₃N/MeCN
116	H	H₂N Me Cis (—)	N	Pale yellow solid	178 ~ 184	[DMSO-d₆] δ ; 0.98(d, J=6.8Hz, 3H), 2.2(brs, 1H), 3.1-3.7(m, 5H), 6.00((s, 2H), 7.98(d, J=13Hz, 1H), 8.94(s, 1H), 9.21(s, 1H)	〃

Example 62

Ethyl 3-(1,2,5-thiadiazol-3-ylmethylamino)-2-(2,4,5-trifluorobenzoyl)acrylate (Compound No.117):

A mixture of ethyl 2,4,5-trifluorobenzoylacetate (492mg), ethyl orthoformate (0.5ml) and acetic anhydride (0.57ml) was stirred at 130 °C for 3 hours. After the solvent was removed in vacuo, a solution of 3-aminomethyl-1,2,5-thiadiazole (0.24g) in benzene (5ml) was added to the residue. The mixture was stirred at room temperature for 24 hours. The precipitate was filtrated. The title compound No. 117 was obtained as a pale yellow solid (530mg).

Melting point: 167.5-170 °C

^{1}H-NMR($CDCl_3$) δ;

0.96 and 1.08(t,J = 7Hz,3H), 3.95-4.15(m,2H), 4.91(d,J = 6.2Hz,2H), 6.8-6.95(m,1H), 7.15-7.4(m,1H), 8.14 and 8.23(d,J = 13.9Hz,1H), 8.54 and 8.56(s,1H)

Example 63

Ethyl 6,7-difluoro-1-(1,2,5-thiadiazol-3-ylmethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.118):

To a solution of compound No.117 (507mg) obtained in Example 62 in tetrahydrofuran (25ml), 55mg of sodium hydride (60% in oil) was added. The solution was stirred for 20 minutes at the room temperature, and the solvent was removed. After addition of an aqueous 5% citric acid solution (10ml), extraction was carried out with chloroform (50ml). The organic phase was dried over Na_2SO_4 and evaporated. After addition of hexane (10ml) to the residue, the precipitate was filtrated. The title compound No. 118 was obtained as a pale yellow solid (0.44g).

Melting point: 198-201 °C

^{1}H-NMR($CDCl_3$) δ;

1.40(t,J = 7Hz,3H), 4.39(q,J = 7Hz,2H), 5.62(s,2H), 7.29(dd,J = 11Hz,J = 6Hz,1H), 8.27(dd,J = 10Hz,J = 9Hz, 1H), 8.56(s,1H), 8.67(s,1H)

Example 64

6,7-Difluoro-1-(1,2,5-thiadiazol-3-ylmethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.119):

Compound No.118 (0.42g) obtained in Example 63 was dissolved in acetic acid (6ml) and 6N-HCl (2ml). The solution was stirred at 100 °C for 2 hours. After cooling, the precipitate was filtrated and washed with water, ethanol and ether. The title compound No. 119 was obtained as a colorless solid (0.325g).

Melting point: 278-281.5 °C

^{1}H-NMR(DMSO-d_5) δ;

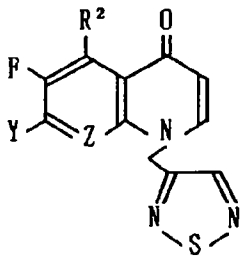
6.19(s,2H), 8.1-8.4(m,2H), 8.97(s,1H), 9.31(s,1H)

Example 65

Compounds Nos. 120-122 listed in Table 29 were synthesized in a similar manner to Example 60, proceeding from the corresponding compound No.119. The results are also shown in Table 29.

Table 29

Compound:



Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
120	H	(S) H_2N N–	C H	Pale yellow solid	241 ~ 245	[DMSO-d_6] δ ; 1.7(brs, 1H), 1.95(brs, 1H), 3.1-3.7 (m, 5H), 6.11(s, 2H), 6.51(d, J=7.8Hz, 1H), 7.77(d, J=14.2Hz, 1H), 8.97(s, 1H), 9.12(s, 1H)	Bt_3N/MeCN
121	H	H_2N N– Me Cis (–)	C H	Pale yellow solid	225 ~ 228.5	[DMSO-d_6] δ ; 0.97(d, J=7.3Hz, 3H), 2.4(brs, 1H), 3.1-3.8(m, 5H), 6.15((s, 2H), 6.57 (d, J=7.8Hz, 1H), 7.81(d, J=14.2Hz, 1H), 9.01(s, 1H), 9.15(s, 1H)	〃
122	H	HN N–	C H	Colorless solid	261 ~ 265	[DMSO-d_6] δ ; 2.81(s, 4H), 3.09(s, 4H), 6.21(s, 2H), 7.06(d, J=7.3Hz, 1H), 7.88(d, J=13.2Hz, 1H), 9.00(s, 1H), 9.23(s, 1H)	〃

Example 66

Ethyl 3-(1,2,5-thiadiazol-3-ylmethylamino)-2-(2,3,4,5-tetrafluorobenzoyl)acrylate (Compound No.123):

A mixture of ethyl 2,3,4,5-tetrafluorobenzoylacetate (528mg), ethyl orthoformate (0.5ml) and acetic anhydride (0.57ml) was stirred at 130 °C for 3 hours. After the solvent was removed in vacuo, a solution of 3-aminomethyl-1,2,5-thiadiazole (0.24g) in benzene (5ml) was added to the residue. The mixture was stirred at room temperature for 40 minutes, and the solvent was removed. To the residue was added 10ml of isopropylether. The precipitate was filtrated. The title compound No. 123 was obtained as a pale yellow solid (600mg).

Melting point: 154-156 °C

^{1}H-NMR($CDCl_3$) δ;

0.98 and 1.11(t,J = 7Hz,3H), 3.95-4.15(m,2H), 4.93(d,J = 6.4Hz,2H), 6.9-7.2(m,1H), 8.20 and 8.27-(d,J = 14Hz,1H), 8.55 and 8.57(s,1H)

Example 67

Ethyl 6,7,8-trifluoro-1-(1,2,5-thiadiazol-3-ylmethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.124):

To a solution of compound No.123 (0.58g) obtained in Example 66 in tetrahydrofuran (20ml), 62mg of sodium hydride (60% in oil) was added. Then the solution was stirred for 0.5 hour at room temperature. The solvent was removed, and the residue was added with an aqueous 5% citric acid solution (10ml). Extraction was carried out with chloroform (50ml). The organic phase was dried (Na_2SO_4) followed by evaporation. The residue was added with isopropylether (10ml), and the precipitate was filtrated. The title compound No. 124 was obtained as a colorless solid (390mg).

Melting point: 200.5-203 °C

^{1}H-NMR($CDCl_3$) δ;

1.41(t,J = 7Hz,3H), 4.41(q,J = 7Hz,2H), 5.76(s,2H), 8.1-8.25(m,1H), 8.58(s,2H)

Example 68

6,7,8-Trifluoro-1-(1,2,5-thiadiazol-3-ylmethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.125):

Compound No.124 (0.38g) obtained in Example 67 was dissolved in acetic acid (4.5ml) and 6N-HCl (1.5ml). The solution was stirred at 100 °C for 1.5 hours. After cooling, ethanol (3ml) was added thereto, and the precipitate was filtrated, followed by washing with ethanol and ether. The title compound No. 125 was obtained as a colorless solid (0.34g).

Melting point: 219.5-222 °C

^{1}H-NMR(DMSO-d_6) δ;

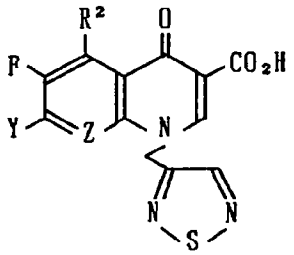
6.2(s,2H),8.1-8.3(m,1H), 8.96(s,1H), 9.27(s,1H)

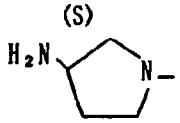
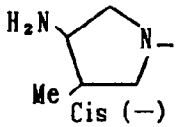
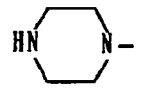
Example 69

Compounds Nos. 126-128 listed in Table 30 were synthesized in a similar manner to Example 68, proceeding from the corresponding compound No.125. The data are also shown in Table 30.

Table 30

Compound:



Compound No.	Group			Property	Melting point (℃)	^{1}H-NMR	Solvent
	R^2	Y	Z				
120	H		C–F	Pale yellow solid	227 ~ 231	[DMSO-d_6] δ; 1.4-1.7(m,1H), 1.8-2.0(m,1H), 3.1-3.8(m,5H), 6.09と6.11(s,合して 2H), 7.74(d, J=14Hz, 1H), 8.91(s,1H), 9.02(s,1H)	Bt_3N/CH_3CN
127	H		C–F	Colorless solid	233.5 ~ 237	[DMSO-d_6] δ; 0.98(d, J=6Hz, 3H), 2.25(brs,1H), 3.4-4.9(m,5H), 6.12(s,2H), 7.75(d, J=14Hz, 1H), 8.93(s,1H), 9.06(s,1H)	〃
128	H		C–F	Colorless solid	227 ~ 228.5	[DMSO-d_6] δ; 2.75(s,4H), 3.11(s,4H), 6.18(s,2H), 7.86(d, J=13Hz, 1H), 8.95(s,1H), 9.14(s,1H)	〃

Example 70

Ethyl 3-(1,2,3-thiadiazol-4-ylmethylamino)-2-(2,4,5-trifluorobenzoyl)acrylate (Compound No.129):

A mixture of ethyl 2,4,5-trifluorobenzoylacetate (418mg), ethyl orthoformate (0.43ml) and acetic anhydride (0.48ml) was stirred at 130 °C for 3 hours. After the solvent was removed in vacuo, a solution of 4-aminomethyl-1,2,3-thiadiazole (0.2g) in benzene (5ml) was added to the residue. The mixture was stirred for 4 hours. The solvent was removed in vacuo. To the residue was added 10ml of isopropylether. The precipitate was filtrated. The title compound No. 129 was obtained as a colorless solid (440mg).

Melting point: 176-178 °C

^{1}H-NMR($CDCl_3$) δ;

0.95 and 1.09(t,J = 7Hz, 3H), 3.9-4.15(m,2H), 5.14(d,J = 6Hz,2H), 6.8-7.0(m,1H), 7.1-7.3(m,1H), 8.18 and 8.29(d,J = 14Hz,1H), 8.49 and 8.51(s,1H)

Example 71

Ethyl 6,7-difluoro-1-(1,2,3-thiadiazol-4-ylmethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.130):

To a solution of compound No.129 (0.44g) obtained in Example 70 in tetrahydrofuran (30ml), 48mg of sodium hydride (60% in oil) was added. Then the solution was stirred for 3 hours at room temperature. The solvent was distilled off, and the residue was added with an aqueous 5% citric acid solution (10ml), followed by extraction with chloroform (50ml). The organic phase was dried over Na_2SO_4 and evaporated. After addition of isopropylether (10ml), the precipitate was filtrated. The title compound No. 130 was obtained as a colorless solid (280mg).

Melting point: 234-237 °C

^{1}H-NMR(DMSO-d_6) δ;

1.30(t,J = 7Hz,3H), 4.25(B,J = 7Hz,2H), 6.11(s,2H), 8.0-8.25(m,2H), 9.06(s,1H), 9.36(s,1H)

Example 72

6,7-Difluoro-1-(1,2,3-thiadiazol-4-ylmethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.131):

Compound No.130 (0.28g) obtained in Example 71 was dissolved in acetic acid (4.5ml) and 6N-HCl (1.5ml). The solution was stirred at 100 °C for 2 hours. After cooling, water (30ml) was added thereto, and the precipitate was filtrated and washed with water, ethanol and ether. The title compound No. 131 was obtained as a pale yellow solid (0.2g).

Melting point: 257-261 °C

^{1}H-NMR(DMSO-d_6) δ;

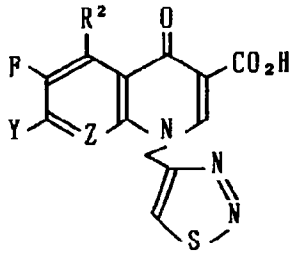
6.30(s,2H), 8.27(dd,J = 10Hz,J = 9Hz,1H), 8.40(dd,J = 12Hz,J = 6.3Hz,1H), 9.41(s,1H), 9.44(s,1H)

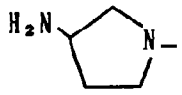
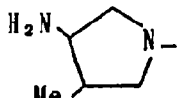
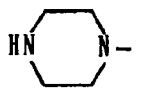
Example 73

Compounds Nos. 132-134 listed in Table 31 were synthesized in a similar manner to Example 73, proceeding from the corresponding compound No.131. The data are also shown in Table 31.

Table 3 1

Compound:



Compound No.	Group			Property	Melting point (℃)	^{1}H-NMR	Solvent
	R^2	Y	Z				
132	H	 (S)	C-H	Yellow solid	251.5 ~ 254	[DMSO-d_6] δ ; 1.7(brs, 1H), 2.0(brs, 1H), 3.1-3.9(m, 5H), 6.22(s, 2H), 6.73(brs, 1H), 7.75(d, J=14Hz, 1H), 9.23(s, 1H), 9.39(s, 1H)	Et_3N/CH_3CN
133	H	 Cis (−)	C-H	Yellow solid	Decomposed from 280	[DMSO-d_6] δ ; 0.99(brs, 3H), 2.2(brs, 1H), 3.1-3.8(m, 5H), 6.22(s, 2H), 6.73(brs, 1H), 7.75(d, J=14Hz, 1H), 9.23(s, 1H), 9.38(s, 1H)	〃
134	H		C-H	Yellow solid	231.5 ~ 234.5	[DMSO-d_6] δ ; 2.84(s, 4H), 3.13(s, 4H), 6.31(s, 2H), 7.33(brs, 1H), 7.88(d, J=13.7Hz, 1H), 9.34(s, 1H), 9.40(s, 1H)	〃

Example 74

Ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-3-(1,3,4-thiadiazol-2-ylamino)acrylate (Compound No.135):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (4.0g), ethyl orthoformate (3.19g) and acetic anhydride (4.39g) was stirred at 130 °C for 2 hours. After the excessive acetic anhydride and ethyl orthoformate were removed in vacuo, the residue was dissolved in chloroform (50ml), to which a methanol solution (100ml) containing 2-amino-1,3,4-thiazole (1.44g) was added and stirred overnight at room temperature. The solvent was removed in vacuo. After dissolved in a small amount of chloroform, hexane was added thereto for solidifying. The precipitate was filtrated. The title compound No. 135 was obtained as a pale yellow solid (5.12g).

Melting point: 137-140.5 °C

^{1}H-NMR($CDCl_3$) δ;

0.98 and 1.19(t,J = 7Hz, 3H), 4.08-4.27(m,2H), 7.45 and 7.58(d,J = 6.8Hz, 1H), 8.68-9.04(m,2H)

Example 75

Ethyl 6-fluoro-7-chloro-1-(1,3,4-thiadiazol-2-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.136):

A solution of compound No.135 (5.12g) obtained in Example 74 and potassium carbonate (1.81g) in dimethylformamide (20ml) was stirred for 15 minutes at 90 °C. After addition of an aqueous 5% citric acid solution (500ml), the precipitate was filtrated and washed with water, ethanol and ether successively. The title compound No. 136 was obtained as a pale yellow solid (3.83g).

Melting point: 201-203 °C

^{1}H-NMR($CDCl_3$) δ;

1.44(t,J = 7Hz,3H), 4.45(q,J = 7Hz,2H), 8.57(d,J = 6.8Hz,1H), 9.21(s,1H), 10.02(s,1H)

Example 76

Ethyl 7-(pyrrolidin-1-yl)-6-fluoro-1-(1,3,4-thiadiazole-2-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.137):

A mixture of compound No.136 (100mg)obtained in Example 75, pyrrolidine (22mg) and triethylamine (33mg) in acetonitrile (10ml) was stirred at 80 °C for 60 minutes. The precipitate was filtrated and washed with ethanol. The title compound was obtained as a pale yellow solid (79mg).

Melting point: 238-242 °C

^{1}H-NMR(DMSO-d_6) δ;

1.32(t,J = 7Hz,3H), 1.99(brs,4H), 3.74(brs,4H), 4.29(q,J = 7Hz,2H), 7.84(d,J = 12.7Hz,1H), 9.48(s,1H), 9.52-(s,1H)

Example 77

7-(Pyrrolidin-1-yl)-6-fluoro-1-(1,3,4-thiadiazole-2-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, sodium salt (Compound No.138):

Compound No.137 (0.05g) obtained in Example 76 was suspended in tetrahydrofuran (20ml), to which an aqueous 1N-NaOH solution (0.13ml) was added. The solution was stirred at room temperature for 3 days. After evaporation of the solvent, chloroform was added. The precipitate was filtrated. The title compound No. 138 was obtained as a pale brown solid (42mg).

Melting point: 253-263 °C

^{1}H-NMR(DMSO-d_6) δ;

1.78(s,4H), 7.68(d,J = 12.7Hz,1H), 9.73(s,1H), 9.87(s,1H)

Example 78

Compounds No. 139-140 were synthesized in a similar manner to Example 77.

The name of compound No. 139, its property, melting point and ^{1}H-NMR data are as follows: Ethyl 6-fluoro-7-(4-methylpiperazin-1-yl)-1-(1,3,4-thiadiazol-2-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.139).

Pale orange solid.

Melting point: 204-206 °C

^{1}H-NMR(DMSO-d_6) δ;

1.31(t,J = 7Hz,3H), 2.24(s,3H), 2.50(brs,4H), 3.77(brs,4H), 4.28(q,J = 7Hz,2H), 8.04(d,J = 13.2Hz, 1H), 9.46(s,1H), 9.59(s,1H)

The name of compound No. 140, its property, melting point and ^{1}H-NMR data are as follows: 6-Fluoro-7-(4-methylpiperazin-1-yl)-1-(1,3,4-thiadiazol-2-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, sodium salt (Compound No.140):

Pale orange solid.

Melting point: 241-246 °C, decomposed

^{1}H-NMR(DMSO-d_6) δ;

2.13(s,3H), 2.24(s,4H), 7.77(d,J = 13.7Hz,1H), 9.74(s,1H), 9.90(s,1H)

Example 79

Ethyl 6,7-difluoro-1-(1,3,4-thiadiazol-2-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.141):

A mixture of ethyl 2,4,5-trifluorobenzoylacetate (9.84g), ethyl orthoformate (10ml) and acetic anhydride (17ml) was stirred at 130 °C for 12 hours. After the solvent was removed in vacuo, a solution of 2-amino-1,3,4-thiadiazole (4.55g) and methanol (30ml) in chloroform (40ml) was added to the residue. The mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo. The residue was purified by chromatography on silicagel (chloroform/ethyl acetate 1:1 as an eluent) to obtain an intermediate of yellow oil (14g). A solution of this oily material (14g) and potassium carbonate (5.4g) in N,N-dimethylformamide (40ml) was stirred for 20 minutes at 100 °C. The solvent was removed in vacuo. After addition of water (200ml) to the residue, the precipitate was filtrated and washed with water, ethanol and ether successively. The title compound No. 141 was obtained as a yellow solid (9.4g).

Melting point: 235-238 °C

^{1}H-NMR(DMSO-d_6) δ;

1.28(t,J = 7Hz,3H), 4.24(q,J = 7Hz,2H), 7.56(dd,J = 11.7Hz, J = 6.3Hz,1H), 8.14(dd,J = 9Hz,J = 10Hz,1H), 8.78(s,1H), 9.88(s,1H)

Example 80

6,7-Difluoro-1-(1,3,4-thiadiazol-2-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.142):

Compound No.141 (0.5g) obtained in Example 79 was dissolved in tetrahydrofuran (70ml). To this solution were added 3ml of water and 0.75ml of 2N-NaOH, then stirred at room temperature for 20 minutes. After evaporation of tetrahydrofuran in vacuo, the residue was neutralized with an aqueous 20% acetic acid solution. The precipitate was filtrated and washed with water, ethanol and ether successively. The title compound No. 142 was obtained as a yellow solid (0.38g).

Melting point: 233-236 °C

^{1}H-NMR(DMSO-d_6) δ;

7.13(dd,J = 12Hz,J = 6.8Hz,1H), 8.15(dd,J = 9Hz,J = 10Hz,1H), 9.87(s,1H), 10.0(s,1H)

Example 81

Ethyl 2-(2,4,5-trifluorobenzoyl)-3-(5-methyl-1,3,4-thiadiazol-2-ylamino)acrylate (Compound No.143):

A mixture of ethyl 2,4,5-trifluorobenzoylacetate (2.18g), ethyl orthoformate (1.97g) and acetic anhydride (4.12g) was stirred at 130 °C for 3 hours. After the excessive acetic anhydride and ethyl orthoformate were removed in vacuo, the residue was dissolved in 50 ml benzene, to which a solution of 2-amino-5-methyl-1,3,4-thiadiazole (1.00g) in methanol (150ml) was added. The mixture was stirred at room temperature for

24 hours. The solvent was removed in vacuo. The residue was purified by chromatography on silicagel (chloroform/ethyl acetate 10:1 as an eluent). The title compound No. 143 was obtained as a colorless solid (1.78g).

Melting point: 147-151 °C

^{1}H-NMR($CDCl_3$) δ;

1.04 and 1.19(t,J = 7Hz,3H); 2.73 and 2.75(s,1H); 4.10-4.28(m,2H); 6.87-7.06(m,1H); 7.30-7.42 and 7.48-7.62(m,1H); 8.34 and 8.70(d,J = 12.7Hz,1H); 11.31(d,J = 12.2Hz,1H)

Example 82

Ethyl 6,7-difluoro-1-(5-methyl-1,3,4-thiadiazol-2-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.144):

To a solution of compound No.143 (1.5g) obtained in Example 81 in tetrahydrofuran (40ml), 0.20g of sodium hydride (60% in oil) was added. Then the solution was stirred for 2 days at room temperature. Tetrahydrofuran was evaporated. The residue was dissolved in chloroform (80ml) and washed with 5% citric acid solution (10ml). The aqueous solution was extracted with chloroform (80ml), followed by dehydration with Glauber's salt. Chloroform was evaporated, and the residue was purified by chromatography on silicagel (chloroform/ethyl acetate 5:1 as an eluent). The title compound No. 144 was obtained as a pale yellow solid (0.85g).

Melting point: 170-173 °C

^{1}H-NMR($CDCl_3$) δ;

1.40(t,J = 7.3Hz,3H); 2.96(s,3H); 4.39(q,J = 7Hz,2H); 7.35(dd,J = 10.7Hz,6.3Hz,1H); 8.28-(dd,J = 8.8Hz,10Hz,1H); 8.58(s,1H)

Example 83

6,7-Difluoro-1-(5-methyl-1,3,4-thiadiazol-2-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, sodium salt (Compound No.145):

Compound No.144 (0.1g) obtained in Example 82 was dissolved in tetrahydrofuran (10ml) and 1N-NaOH (0.3ml). The solution was stirred at room temperature overnight. After addition of chloroform, the precipitate was filtrated, followed by washing with chloroform. The title compound No. 145 was obtained as a pale yellow solid (77mg).

Melting point: Colored from 255 °C, decomposed 295 °C

^{1}H-NMR(DMSO-d_6) δ;

2.80(s,3H); 7.02(dd,J = 12.7Hz,6.8Hz,1H); 7.92(dd, J = 10.7Hz,9.3Hz,1H); 9.97(s,1H)

Example 84

Ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-3-(5-methyl-1,3,4-thiadiazol-2-ylamino)acrylate (Compound No.146):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (4.00g), ethyl orthoformate (3.18g) and acetic anhydride (4.38g) was stirred at 130 °C for 2 hours. After the excessive acetic anhydride and ethyl orthoformate were removed in vacuo, the residue was dissolved in 40ml chloroform, to which a solution of 2-amino-5-methyl-1,3,4-thiadiazole (1.61g) in methanol (180ml) was added. The mixture was stirred at room temperature overnight. The solvent was removed in vacuo. The residue was purified by chromatography on silicagel (chloroform/ethyl acetate 10:1 then 5:1 as an eluent). The title compound No. 146 was obtained as a pale yellow solid (4.37g).

Melting point: 142-152 °C decomposed

^{1}H-NMR($CDCl_3$) δ;

0.97 and 1.17(t,J = 7Hz,3H); 2.76 and 2.87(s,3H); 4.07-4.25(m,2H); 7.44 and 7.56(d,J = 7Hz,1H); 8.63 and 8.87(s,1H)

Example 85

Ethyl 6-fluoro-7-chloro-1-(5-methyl-1,3,4-thiadiazol-2-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.147):

To a solution of compound No.146 (4.1g) obtained in Example 84 in tetrahydrofuran (100ml), 0.49g of sodium hydride (60% in oil) was added. Then the solution was stirred for 1 day at room temperature. Tetrahydrofuran was removed and the residue was dissolved in chloroform (200ml), followed by washing with 5% citric acid solution and dried over Na_2SO_4.
Chloroform was evaporated, and the residue was suspended in hexane, and the solid was filtrated. The title compound No. 147 was obtained as an orange solid (3.53g).

Melting point: 159-162 °C

^{1}H-NMR($CDCl_3$) δ;

1.43(t,J = 7Hz,3H); 2.86(s,3H); 4.44(q,J = 7Hz,2H); 8.55(d,J = 7.3Hz,1H); 9.89(s,1H)

Example 86

Ethyl 7-(3-(S)-aminopyrrolidin-1-yl)-6-fluoro-1-(5-methyl-1,3,4-thiadiazol-2-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.148):

A mixture of compound No.147 (100mg), 3-(S)-aminopyrrolidine (33mg) and triethylamine (39mg) in acetonitrile (10ml) was stirred at 80 °C for 60 minutes. After cooling, the precipitate was filtrated and washed with ethanol. The title compound No. 148 was obtained as a pale orange solid (73mg).

Melting point: 265-268 °C

^{1}H-NMR(D_2O) δ;

1.35(t,J = 7Hz,3H); 2.71(s,3H);4.26(q,J = 7Hz,2H); 7.59(d,J = 12.2Hz,1H); 8.90(s,1H)

Example 87

7-(3-(S)-Aminopyrrolidin-1-yl)-6-fluoro-1-(5-methyl-1,3,4-thiadiazol-2-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, sodium salt (Compound No.149):

Compound No.148 (0.05g) obtained in Example 86 was dissolved in water (3ml) and 1N-NaOH (0.1ml). The solution was stirred at room temperature for 24 hours. After evaporation of water, chloroform was added. The precipitate was filtrated. The title compound No. 149 was obtained as a pale orange solid (18mg).

Melting point: Colored from 200 °C, decomposed 280 °C

^{1}H-NMR(D_2O) δ;

2.0-2.3(brs,1H); 2.43(s,3H); 3.6(brs,1H); 7.25 (d,J = 12.7Hz,1H); 8.85(s,1H)

Example 88

Ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-3-(5-trifluoromethyl-1,3,4-thiadiazol-2-ylamino)acrylate (Compound No.150):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (2.8g), ethyl orthoformate (2.6ml) and acetic anhydride (2.8ml) was stirred at 130 °C for 6 hours. After the solvent was removed in vacuo, a solution of 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (1.69g) in chloroform (20ml) and ethanol (8ml) was added to the residue. The mixture was stirred at room temperature for 4 hours. The solvent was removed in vacuo. The residue was purified by chromatography on silicagel (chloroform/ethyl acetate 50:1 as an eluent). The title compound No. 150 was obtained as a yellow waxy solid (4.5g).

Melting point: 73-76 °C

^{1}H-NMR($CDCl_3$) δ;

0.98 and 1.19(t,J = 7Hz,3H), 4.05-4.25(m,2H), 7.47 and 7.62(d,J = 7.4Hz,1H), 8.67 and 8.91-(d,J = 12Hz,1H)

Example 89

Ethyl 7-chloro-6-fluoro-1-(5-trifluoromethyl-1,3,4-thiadiazole-2-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.151):

A solution of compound No.150 (4.3g) obtained in Example 88 and sodium hydrogencarbonate (0.79g) in N,N-dimethylformamide (30ml) was stirred for 15 minutes at 100 °C. The solvent was removed in vacuo, and extracted with chloroform (200ml). The organic phase was washed with water. The organic layer was dried over Na_2SO_4 and evaporated. The residue was added with ether (20ml) and the precipitate was filtrated. The title compound No. 151 was obtained as a colorless solid (3.2g).

Melting point: 177.5-178.5 °C

^{1}H-NMR($CDCl_3$) δ;

1.44(t,J = 7Hz,3H), 4.46(q,J = 7Hz,2H), 8.58(d,J = 6.8Hz,1H), 10.0(s,1H)

Example 90

7-Chloro-6-fluoro-1-(5-trifluoromethyl-1,3,4-thiadiazole-2-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.152):

Compound No.151 (30mg) obtained in Example 89 was dissolved in a mixture of acetic acid (2ml) and HCl (0.5ml). The solution was stirred at 100 °C for 0.5 hour. After cooling and addition of water (4ml), the precipitate was filtrated and washed with ethanol, ether and n-hexane. The title compound No. 152 was obtained as a colorless solid (13mg).

Melting point: 232-237 °C

^{1}H-NMR(DMSO-d_5) δ;

8.81(d,J = 7Hz,1H), 9.79(s,1H)

Example 91

6-Fluoro-7-(pyrrolidin-1-yl)-1-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.153):

A mixture of compound No.151 (200mg) obtained in Example 89 and pyrrolidine (67mg) in chloroform (5ml) was stirred at room temperature for 15 minutes. After evaporation of the solvent, ethanol (10ml) was added. The precipitate was filtrated to obtain a colorless solid (170mg). 50mg of the obtained solid was taken and dissolved in tetrahydrofuran (3ml), to which 6N-HCl (0.3ml) was added. After stirring for 1 day at room temperature, the precipitate was filtrated and washed with water, ethanol and ether. The title compound No. 153 was obtained as a yellow solid (30mg).

Melting point: 239.5-241 °C

^{1}H-NMR(DMSO-d_5) δ;

2.04(brs,4H), 3.84(brs,4H), 8.04(d,J = 12.7Hz,1H), 9.63(s,1H)

Example 92

Ethyl 2-(2,4,5-trifluorobenzoyl)-3-(5-trifluoromethyl -1,3,4-thiadiazol-2-ylamino)acrylate (Compound No.154):

A mixture of ethyl 2,4,5-trifluorobenzoylacetate (2.46g), ethyl orthoformate (2.6ml) and acetic anhydride (2.8ml) was stirred at 130 °C for 6 hours. After the solvent was removed in vacuo, a solution of 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (1.69g) and ethanol (5ml) in chloroform (20ml) was added to the residue. The mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo. The residue was purified by chromatography on silicagel (chloroform/ethyl acetate 50:1 as an eluent). The title compound No. 154 was obtained as a yellow oil (2.3g).

^{1}H-NMR($CDCl_3$) δ;

1.05 and 1.21(t,J = 7Hz,3H), 4.1-4.3(m,2H), 6.85-7.05(m,1H), 7.35-7.45 and 7.52-7.7(m,1H), 8.36-8.73-(d,J = 12Hz,1H)

Example 93

Ethyl 6,7-difluoro-1-(5-trifluoromethyl-1,3,4-thiadiazole-2-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.155):

A solution of compound No.154 (2.3g) obtained in Example 92 and potassium carbonate (0.75g) in N,N-dimethylformamide (20ml) was stirred for 10 minutes at 100 °C. The solvent was removed in vacuo. After extraction with chloroform, the organic phase was washed with water, dried (Na_2SO_4) and evaporated. After addition of hexane (50ml) to the residue, the precipitate was filtrated. The title compound was obtained as a red solid (1.1g).

Melting point: 130-136 °C

^{1}H-NMR($CDCl_3$) δ;

1.37(t,J = 7Hz,3H), 4.33(q,J = 7Hz,2H), 7.46(dd, J = 10.7Hz,J = 6.4Hz,1H), 8.13(dd,J = 9.8Hz,J = 8.5Hz,1H), 8.55(s,1H)

Example 94

6,7-Difluoro-1-(5-trifluoromethyl-1,3,4-thiadiazole-2-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.156):

Compound No.155 (30mg) obtained in Example 93 was dissolved in a mixture of acetic acid (2ml) and HCl (0.5ml). The solution was stirred at 100 °C for 40 minutes. After allowed to be cooled, water (4ml) was added to the reaction mixture, and the precipitate was filtrated and washed with ethanol, ether and n-hexane. The title compound No. 156 was obtained as a pale orange solid (18mg).

Melting point: 272-276 °C

^{1}H-NMR(DMSO-d_6) δ;

7.96(dd,J = 12Hz,J = 6Hz,1H), 8.33(dd,J = 9Hz,J = 10Hz,1H), 9.25 (s,1H)

Example 95

Ethyl 3-(1,2,5-thiadiazole-3-ylamino)-2-(2-methyl-3,4,6-trifluorobenzoyl)acrylate (Compound No.157):

Compound No. 157 (colorless needles) was prepared in a similar manner to Example 17, proceeding from the corresponding compounds ethyl 2-methyl-3,4,6,-trifluorobenzoylacetate, ethyl orthoformate, acetic anhydride and 3-amino-1,2,5-thiadiazole hydrochloride.

Melting point: 134-136 °C

^{1}H-NMR($CDCl_3$) δ;

1.14(t,J = 7Hz,3H), 2.22(d,J = 3Hz,3H), 4.13(q,J = 7Hz,2H), 6.80(dt,J = 10Hz,6Hz,1H), 8.36(s,1H), 9.00-(d,J = 12Hz,1H)

Example 96

Ethyl 5-methyl-6,7-difluoro-1-(1,2,5-thiadiazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.158):

Compounds No. 158 which is a pale yellow solid was prepared in a similar manner to Example 18, proceeding from the corresponding compound No.157.

Melting point: 208-213 °C

^{1}H-NMR($CDCl_3$) δ;

1.38(t,J = 7Hz,3H), 2.89(d,J = 3Hz,3H), 4.39(q,J = 7Hz,2H), 6.86(dd,J = 11Hz,7Hz,1H), 8.46(s,1H), 8.79-(s,1H)

Example 97

5-Methyl-6,7-difluoro-1-(1,2,5-thiadiazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.159):

Compounds No. 159 which is a colorless solid was prepared in a similar manner to Example 19, proceeding from the corresponding compound No.158.

Melting point: 264-268 °C decomposed

^{1}H-NMR(DMSO-d_6) δ;

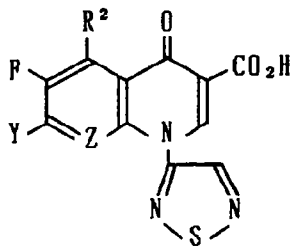
2.87(d,J = 3Hz,3H), 7.58(dd,J = 7Hz,J = 12Hz,1H), 9.07(s,1H),9.22(s,1H)

Example 98

Compounds Nos. 160-163 listed in Tables 32 and 33 were synthesized in a similar manner to Example 4, proceeding from the compound No.159 obtained in Example 97.

Table 3 2

Compound :



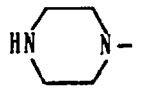
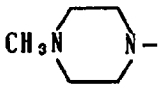
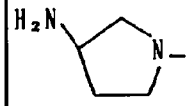
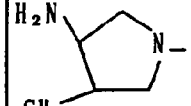
Compound No.	Group			Property	Melting point (℃)	^{1}H-NMR	Solvent
	R^2	Y	Z				
160	CH_3		C–H	Colorless solid	194 ~ 198	[DMSO-d_6] δ ; 2.64(brs, 4H), 2.80(d, J=3Hz, 3H), 3.03(brs, 4H), 6.52(d, J=7Hz, 1H), 8.89(s, 1H), 9.30(s, 1H)	CH_3CN Et_3N
161	CH_3		C–H	Colorless solid	243 ~ 247	[DMSO-d_6] δ ; 2.20(s, 3H), 2.42(brs, 4H), 2.80(d, J=3Hz, 3H), 3.12(brs, 4H), 6.57(d, J=8Hz, 1H), 8.93(s, 1H), 9.31(s, 1H)	〃

Table 33

Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
162	CH_3	 (S)	C H	Pale yellow solid	205 ~ 208	[DMSO-d_6] δ : 1.58-1.72(m, 1H), 1.88-2.03(m, 1H), 2.77(brs, 3H), 3.05~3.15(m, 1H), 3.28-3.60(m), 5.99(d, J=8Hz, 1H), 8.82(s, 1H), 9.29(s, 1H)	CH_3CN Et_3N
163	CH_3	 Cis (−)	C H	Pale yellow solid	242 ~ 245	[DMSO-d_6] δ : 0.94(d, J=7Hz, 3H), 2.09-2.23(m, 1H), 2.75(brs, 1H), 3.10-3.62(m), 5.95(d, J=8Hz, 1H), 8.82(s, 1H), 9.28(s, 1H)	〃

Example 99

Ethyl 7-chloro-6-fluoro-1-(1,2,4-thiadiazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.164):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (4.2g), ethyl orthoformate (3.9ml) and acetic anhydride (4.3ml) was stirred at 135 °C for 2 hours. After the solvent was removed in vacuo, the residue was added with chloroform (20ml) and ethanol (10ml). 5-Amino-1,2,4-thiadiazole (1.51g) was added thereto and allowed to react for 8 hours. The solvent was removed. The residue was added with n-hexane, and the precipitate was filtrated. 4.1 g of a yellow solid was obtained. 3.5 g was taken therefrom and dissolved in dimethylformamide (35ml). 0.36 g of sodium hydride (60% in oil) was added thereto and allowed to react at 100 °C for 5 minutes. The solvent was removed. After addition of water to the residue, the insoluble matter was filtrated and washed with water, ethanol, ether and n-hexane successively. The title compound No. 164 was obtained as a pale yellow solid (2.5g).

Melting point: 203-206 °C

^{1}H-NMR($CDCl_3$) δ;

1.34(t,J = 7Hz,3H), 4.34(q,J = 7Hz,2H), 8.71(d,J = 8Hz,1H), 8.85(s,1H), 9.71(s,1H)

Example 100

7-Chloro-6-fluoro-1-(1,2,4-thiadiazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.165):

Compound No.164 (1.1g) obtained in Example 99 was dissolved in a mixture of tetrahydrofuran (40ml) and c-HCl (10ml). The solution was stirred at 80 °C for 1.5 hour. After the solvent was removed in vacuo, the precipitate was filtrated and washed with ethanol, ether and n-hexane. The title compound No. 165 was obtained as a slightly yellow solid.

Melting point: 278-282 °C

^{1}H-NMR(DMSO-d_6) δ;

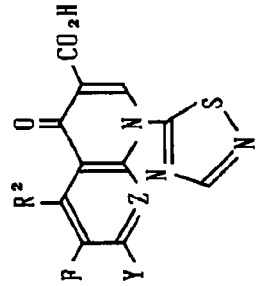
8.82(d,J = 7Hz,1H), 8.88(s,1H), 9.81(s,1H)

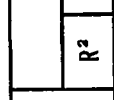
Example 101

Compounds Nos. 166-167 listed in Table 34 were synthesized in a similar manner to Example 41, proceeding from the compound No.164 obtained in Example 99.

Table 34

Compound:



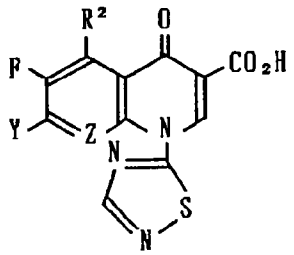
Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
166	H	S form · HCl	N	Dim yellow solid	Colored from 285, decomposed	[DMSO-d₆] δ : 2.28-2.50(m,2H), 4.05-4.18(m,3H), 8.18(d,J=13Hz,1H), 8.49(brs,3H), 9.53(s,1H), 9.73(s,1H)	$CHCl_3$ Et_3N → 6NHCl
167	H	 · HCl シス (—)	N	Pale yellow solid	Colored from 225, decomposed	[DMSO-d₆] δ : 1.18(d,J=6Hz,3H), 1.49-1.57(m,1H), 1.69-1.77(m,1H), 3.80-4.48(m,4H), 8.19(d,J=13Hz,1H), 8.87(s,1H), 9.75(s,1H)	$CHCl_3$ Et_3N → 6NHCl

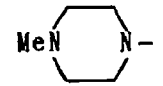
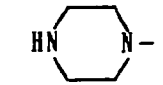
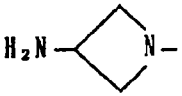
Example 102

Compounds Nos. 168-170 listed in Table 35 were synthesized in a similar manner to Example 11, proceeding from the compound No.165 obtained in Example 100.

Table 3 5

Compound:



Compound No.	Group			Property	Melting point (℃)	^{1}H-NMR	Solvent
	R^2	Y	Z				
168	H	 · HCl	N	Dim yellow solid	Colored from 290, decomposed	[DMSO-d_6] δ ; 2.49(s, 3H), 2.84(brs, 4H), 8.38(d, J=13Hz, 1H), 8.89(s, 1H), 9.83(s, 1H)	MeCN Et_3N ↓ 6N-HCl
169	H	 · HCl	N	Pale brown solid	Colored from 280, decomposed	[DMSO-d_6] δ ; 3.43(brs, 4H), 4.38(brs, 4H), 8.37(d, J=13Hz, 1H), 8.90(s, 1H), 9.20(brs, 2H), 9.83(s, 1H)	MeCN Et_3N ↓ 6N-HCl
170	H	 · HCl	N	Dim yellow solid	Colored from 278, decomposed	[DMSO-d_6] δ ; 4.30(brs, 1H), 4.63-4.85(m, 4H), 8.23(d, J=13Hz, 1H), 8.68(brs, 3H), 8.88(s, 1H), 9.74(s, 1H)	MeCN Et_3N ↓ 6N-HCl

Example 103

Ethyl 6,7-difluoro-1-(1,2,4-thiadiazol-5-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.171):

A mixture of ethyl 2,4,5-trifluorobenzoylacetate (3.7g), ethyl orthoformate (3.9ml) and acetic anhydride (4.3ml) was stirred at 135 °C for 3 hours. After the solvent was removed in vacuo, a solution of 5-amino-1,2,4-thiadiazole (1.51g) in chloroform (20ml) and ethanol (10ml) was added to the residue. The mixture was stirred at room temperature for 8 hours. The solvent was removed. The residue was purified by column chromatography on silicagel (chloroform/ethyl acetate 4:1 as an eluent) to obtain 4.4g of a yellow oil. A solution of this oil (4g) and sodium hydride(0.45g) in dimethylformamide (40ml) was stirred for 5 minutes at 100 °C. The solution was removed. Chloroform and water were added to the residue, and the organic phase was extracted. After evaporation of the solvent, the residue was added with ethanol, and the precipitate was filtrated, washed with ethanol, ether and n-hexane successively. The title compound No. 171 was obtained as a yellow solid (1.5g).

Melting point: 149-152 °C

^{1}H-NMR($CDCl_3$) δ;1.42(t,J = 7Hz,3H), 4.43(q,J = 7Hz,2H), 8.23-8.33(m,2H), 8.71(s,1H), 8.79(s,1H)

Example 104

6,7-Difluoro-1-(1,2,4-thiadiazol-5-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.172):

Compound No.171 (0.7g) was dissolved in a mixture of tetrahydrofuran (28ml) and c-HCl (7ml). The solution was stirred at 80 °C for 1 hour. After evaporation of the solvent, the residue was added with ethanol. The precipitate was filtrated and washed with ethanol, ether and n-hexane. The title compound No. 172 was obtained as a brown solid (0.56g).

Melting point: 212-216 °C

^{1}H-NMR(DMSO-d_6) δ;

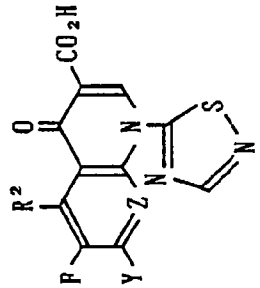
7.99(dd,J = 6Hz,J = 12Hz,1H), 8.34(dd,J = 9Hz,J = 10Hz,1H), 9.08(s,2H)

Example 105

Compound No. 173 listed in Table 36 was prepared in a similar manner to Example 4, proceeding from the compound No.172.

Table 36

Compound:



Compound No.	Group			Property	Melting point (℃)	^{1}H-NMR	Solvent
	R^2	Y	Z				
173	H		C 1 H	Pale brown solid	145 ~ 147	[DMSO-d_6] δ : 1.93(brs, 4H), 3.48(brs, 4H), 6.71(d, J=7Hz, 1H), 7.85(d, J=15Hz, 1H), 8.92(s, 1H), 9.06(s, 1H)	MeCN Et_3N

Example 106

Ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-3-(1H-tetrazol-5-ylamino)acrylate (Compound No.174):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (5.6g), ethyl orthoformate (5.2ml) and acetic anhydride (5.6ml) was stirred at 130 °C for 4 hours. After the solvent was removed in vacuo, a solution of 5-amino-1H-tetrazole (1.7g) in benzene (20ml) and methanol (40ml) was added to the residue. The mixture was stirred at room temperature for 5 hours. The solvent was removed. After addition of hexane (100ml) to the residue, stirring was carried out for 1 hour. The precipitate was filtrated. The title compound No. 174 was obtained as a colorless solid (6.5g).

Melting point: 150.5-152 °C

^{1}H-NMR(DMSO-d_6) δ;

1.05(t,J = 7Hz,3H), 3.9-4.15(m,2H), 7.93(s,1H), 8.24 and 8.60(d,J = 8Hz,1H), 8.79(s,1H)

Example 107

Ethyl 7-chloro-6-fluoro-1-(1H-tetrazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.175):

A solution of compound No.174 (3g) obtained in Example 106 and potassium carbonate (1.1g) in N,N-dimethylformamide (20ml) was stirred for 1 hour at 110 °C. The solution was removed in vacuo. After addition of 6N-HCl (30ml) to the residue, the precipitate was filtrated and washed with water, ethanol and ether successively. The title compound No. 175 was obtained as a yellow solid (2.7g).

Melting point: 202-207 °C

^{1}H-NMR(DMSO-d_5) δ;

1.28(t,J = 7Hz,3H), 4.26(q,J = 7Hz,2H), 8.57(d,J = 7.7Hz,1H), 8.92(s,1H)

Example 108

7-Chloro-6-fluoro-1-(1H-tetrazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.176):

Compound No.175 (1.2g) obtained in Example 107 was dissolved in a mixture of acetic acid (5ml) and 6N-HCl (5ml). The solution was stirred at 100 °C for 2 hours. After evaporation of the solvent in vacuo, 5ml of ethanol was added to the residue. The precipitate was filtrated and washed with ether. The title compound No. 176 was obtained as a pale yellow solid (0.68g).

Melting point: 270 °C or more, colored and decomposed

^{1}H-NMR(DMSO-d_5) δ;

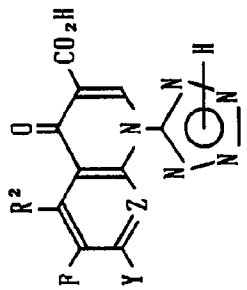
8.74(d,J = 7.2Hz,1H), 9.07(s,1H)

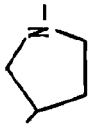
Example 109

Compounds No. 177 listed in Table 37 was synthesized in a similar manner to Example 4, proceeding from the compound No.176 obtained in Example 108.

Table 37

Compound:



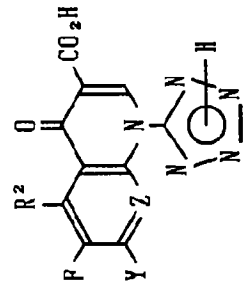
Compound No.	Group			Property	Melting point (℃)	^{1}H-NMR	Solvent
	R^2	Y	Z				
177	H	(S) 	N	Pale yellow solid	Colored from 250, decomposed	[DMSO-d_6] δ : 1.5-1.8(m, 1H), 1.8-2.05(m, 1H), 2.7-3.2(m, 4H), 8.0(d, J=12.8Hz, 1H), 8.44(s, 1H)	MeCN+DMF Et_3N

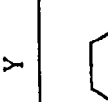
Example 110

Compounds Nos. 178-179 listed in Table 38 were synthesized in a similar manner to Example 11, proceeding from the compound No.177 obtained in Example 109.

Table 38

Compound:



Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
178	H	· HCl	N	Colorless solid	300 or more	[DMSO-d₆] δ ; 3.14(brs, 4H), 3.82(brs, 4H), 8.24(d, J=12.8Hz, 1H), 8.94(s, 1H), 9.57(brs, 2H),	MeCN+DMF → Et₃N → 6N-HCl
179	H	 · HCl	N	Colorless solid	Colored from 285, decomposed	[DMSO-d₆] δ ; 2.74(s, 3H), 3.10(brs, 2H), 3.3-3.6(br, 4H), 4.15-4.4(br, 2H), 8.27(d, J=12.8Hz, 1H), 8.97(s, 1H)	〃

Example 111

Ethyl 6,7-difluoro-1-(1H-tetrazol-5-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.180):

A mixture of ethyl 2,4,5-trifluorobenzoylacetate (9.8g), ethyl orthoformate (10ml) and acetic anhydride (17ml) was stirred at 130 °C for 4 hours. After the solvent was removed in vacuo, a solution of 5-amino-1H-tetrazole (3.4g) in benzene (20ml) and methanol (80ml) was added to the residue. The mixture was stirred at 60 °C for 20 minutes. The solvent was removed in vacuo. After addition of hexane (100ml) to the residue, the precipitate was filtrated to obtain 7g of a colorless solid. A solution of this solid (7.0g) and potassium carbonate (5.5g) in N,N-dimethylformamide (40ml) was stirred for 1 hour at 100 °C. The solution was removed in vacuo. 6N-HCl (30ml) was added to the residue and stirred for 10 minutes. The precipitate was filtrated and washed with water, ethanol and ether successively. The title compound No. 180 was obtained as a yellow solid (4g).

Melting point: 233-236.5 °C

^{1}H-NMR(DMSO-d_6) δ;

1.29(t,J = 7Hz,3H), 4.26(q,J = 7Hz,2H), 7.99(dd,J = 12Hz,6.3Hz,1H), 8.15(dd,J = 10.7Hz,8.5Hz,1H), 8.90-(s,1H)

Example 112

6,7-Difluoro-1-(1H-tetrazol-5-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.181):

Compound No.180 (2g) obtained in Example 111 was dissolved in a solution of acetic acid (10ml) and 6N-HCl (10ml). The solution was stirred at 100 °C for 1 hour, and the solvent was removed. After addition of water (100ml) to the residue, the precipitate was filtrated and washed with ethanol and ether. The title compound No. 181 was obtained as a pale yellow solid (1.1g).

Melting point: 246-249 °C

^{1}H-NMR(DMSO-d_6) δ;

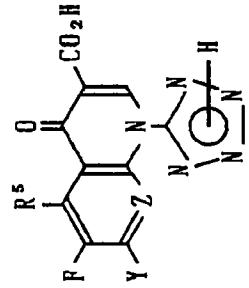
8.14 (dd,J = 12Hz,6.4Hz,1H), 8.31(dd,J = 10Hz,9Hz,1H), 9.13(s,1H)

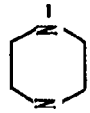
Example 113

Compounds Nos. 182-183 listed in Table 39 were synthesized in a similar manner to Example 11, proceeding from the compound No.181 in Example 112.

Table 39

Compound:



Compound No.	Group R²	Group Y	Group Z	Property	Melting point (℃)	¹H-NMR	Solvent
182	H	 · HCl	C—H	Colorless solid	Colored from 280, decomposed	[DMSO-d_6] δ ; 3.27(s, 4H), 3.40(s, 4H), 7.64(d, J=6.4Hz, 1H), 8.0(d, J=13.3Hz, 1H), 9.02(s, 1H), 9.24(brs, 2H)	DMF Et_3N ↓ 6N-HCl
183	H	(S) · HCl	C—H	Yellow solid	Colored from 270, decomposed	[DMSO-d_6] δ ; 1.95-2.2(m, 1H), 2.2-2.4(m, 1H), 3.45-4.05(m, 5H), 7.19(d, J=6.8Hz, 1H), 7.89(d, J=14.1Hz, 1H), 8.15(brs, 3H), 8.90(s, 1H)	〃

Example 114

Ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-3-(4-methyl-1,2,5-thiadiazol-3-ylamino)acrylate (Compound No.184):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (14.9g), ethyl orthoformate (13.3ml) and acetic anhydride (15ml) was stirred at 130 °C for 3 hours. After the solvent was removed in vacuo, a solution of 3-amino-4-methyl-1,2,5-thiadiazole hydrochloride (7.7g) and triethylamine (5.2g) in chloroform (80ml) was added to the residue. The mixture was stirred at room temperature for 1 hour. The solvent was removed in vacuo. The residue was purified by column chromatography on silicagel (chloroform as an eluent). The title compound No. 184 was obtained as a yellow oil (20g).

^{1}H-NMR($CDCl_3$) δ;

0.98 and 1.18(t,J = 7Hz,3H), 2.60 and 2.64(s,3H), 4.08-4.21(m,2H), 7.43 and 7.56(d,J = 7Hz,1H), 8.98 and 9.06(d,J = 12.6Hz,1H)

Example 115

Ethyl 7-chloro-6-fluoro-1-(4-methyl-1,2,5-thiadiazol-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.185):

To a solution of compound No.184 (20g) obtained in Example 114 in tetrahydrofuran (500ml), 2.04g of sodium hydride(60% in oil) was added at room temperature. Then the solution was stirred for 0.5 hour at 70 °C. After addition of 5% citric acid solution to make the system acidic, tetrahydrofuran was removed. Extraction was carried out with chloroform (500ml). The organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silicagel (chloroform/ethyl acetate 10:1 as an eluent). The title compound No. 185 was obtained as a colorless solid (15.1g).

Melting point: 191.5-192.5 °C

^{1}H-NMR($CDCl_3$) δ;

1.41(t,J = 7Hz,3H), 2.42(s,3H), 4.41(q,J = 7Hz,2H), 8.50(d,J = 7Hz,1H), 8.65(s,1H)

Example 116

7-Chloro-6-fluoro-1-(4-methyl-1,2,5-thiadiazol-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.186):

Compound No.185 (15.1g) obtained in Example 115 was dissolved in acetic acid (180ml) and c-HCl (80ml). The solution was stirred for 1 hour with heating under reflux. After cooling, water (200ml) was added thereto. The precipitate was filtrated and washed with water, ethanol and ether. The title compound No. 186 was obtained as pale yellow needles (13.3g).

Melting point: 247-249 °C

^{1}H-NMR(DMSO-d_6) δ;

2.35(s,3H), 8.78(d,J = 7.7Hz,1H), 9.17(s,1H)

Example 117

7-(3-(S)-Aminopyrrolidin-1-yl)-6-fluoro-1-(4-methyl-1,2,5-thiadiazol-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrochloride (Compound No.187):

A mixture of compound No.186 (12g), triethylamine (7.1g) and 3-(S)-aminopyrrolidine (4.47g) in acetonitrile (240ml) was stirred at 80 °C for 180 minutes. After cooling, the precipitate was filtrated and washed with ethanol, followed by adding to a mixture of 200ml of 6N-HCl and 150ml of acetic acid and heating until dissolved. After the solvent was removed in vacuo, ethanol was added. The precipitate was collected by filtration and washed with ethanol and ether. The title compound was obtained as a pale yellow solid (15.6g). A water/ethanol (1:1) solution was used for reprecipitation to obtain the title compound No. 187 in a colorless solid (9.8g).

Melting point: 278 °C decomposed

^{1}H-NMR(DMSO-d_6) δ;

1.95-2.30(br,2H), 2.37(s,3H), 3.7-4.2(br,2H), 8.12(d,J = 12.4Hz,1H), 8.4(brs,3H), 8.96(s,1H)

This compound can also be obtained as slightly yellow needles by crystallizing from water. It

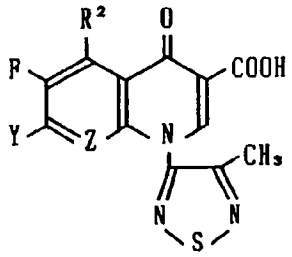
decomposes at a temperature of 299 °C or higher.

Example 118

Compounds Nos. 188-193 listed in Tables 40 and 41 were synthesized in a similar manner to Example 117.

Table 40

Compound:



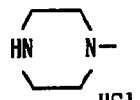
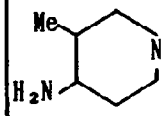
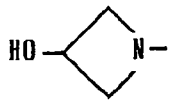
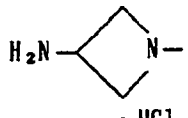
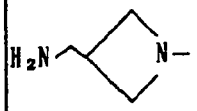
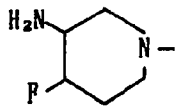
Compound No.	R^2	Y	Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
188	H	 · HCl	N	Pale yellow solid	Decomposed from 286	[DMSO-d_6] δ ; 2.34(s, 3H), 3.12(s, 4H) 3.74(s, 4H), 8.23(d, J=12.8Hz, 1H), 9.04(s, 1H), 9.65(brs, 2H)	Et_3N/CH_3CN ↓ AcOH, 6N-HCl
189	H	 (3S, 4S) · HCl	N	Colorless solid	Decomposed from 293	[DMSO-d_6] δ ; 1.03(d, J=6Hz, 3H), 2.37(s, 3H), 2.45-2.7(brs, 1H), 3.2-4.2(m, 5H), 8.13(d, J=12.4Hz, 1H), 8.25(brs, 3H), 8.95(s, 1H)	〃
190	H		N	Colorless solid	191.5	[DMSO-d_6] δ ; 2.34(s, 3H), 3.5-4.6(m, 6H), 7.98(d, J=11.6Hz, 1H), 8.70(s, 1H)	Et_3N CH_3CN (no acid treatment)

Table 4 1

Compound No.	R^2	Y	Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
191	H	 · HCl	N	Colorless solid	237— 239.5	[DMSO-d_6] δ ; :2.35(s, 3H), 3.8-4.95(m, 4H), 8.15(d, J=11.6Hz, 1H), 8.59(brs, 3H), 8.96(s, 1H)	Et_3N/CH_3CN ↓ AcOH, 6N-HCl
192	H		N	Pale yellow solid	214-218	[DMSO-d_6] δ ; 2.35(s, 3H), 2.7-3.15(m, 3H), 3.6-4.5(m, 4H), 7.99(d, J=11.1Hz, 1H), 8.82(s, 1H)	Et_3N CH_3CN (no acid treatment
193	H	 trans	N	Pale yellow solid	Decomposed from 278	[DMSO-d_6] δ ; 2.36(s, 3H), 4.9-5.2(m, 1H), 8.13(d, J=11.1Hz, 1H), 8.97(s, 1H)	〃

Example 119

Benzyl 6,7-difluoro-1-(1,2,4-triazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.194):

A mixture of benzyl 2,4,5-trifluorobenzoylacetate (1.5g), ethyl orthoformate (1.08g) and acetic anhydride (2.24g) was stirred at 130 °C for 3 hours. After the excessive acetic anhydride and ethyl orthoformate were removed in vacuo, a solution of 3-amino-1,2,4-triazole (0.41g) in methanol (25ml) was added to the residue. The mixture was stirred at room temperature for 3 days. The solvent was removed. The residue was purified with a silicagel column (chloroform/ethyl acetate 10:1 - 5:1 as an eluent). The title compound was obtained as pale yellow needles (1.10g).

Melting point: 116-124 °C

^{1}H-NMR(DMSO-d_6) δ;

5.23(d,J = 4.9Hz,2H), 7.22-7.41(m,5H), 7.58-7.70(m,1H), 7.74-7.88(m,1H), 8.80(s,1H), 9.42(s,1H)

Example 120

6,7-Difluoro-1-(1,2,4-triazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.195) and 6,7-difluoro-1-(N-benzyl-1,2,4-triazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.196):

To a solution of compound No.194 (1.02g) in tetrahydrofuran (50ml) was added a solution of Pd/C (300mg) in ethanol (50ml), then stirred under H2 gas atmosphere for 1 day. After removing the catalyst with a membrane filter, the filtrate was evaporated. The residue was purified with a silicagel column (chloroform/ethyl acetate 1:1 as an eluent). A colorless solid No. 195 was first obtained (53mg), and next, a colorless solid of N-benzyl, No. 196 was obtained (95mg).

The melting point and the ^{1}H-NMR data of the compound 195 are as follows:

Melting point: 170-177 °C

^{1}H-NMR(DMSO-d_6) δ;

7.79-7.98(m,2H), 8.79(s,1H), 9.38(s,1H)

The melting point and the ^{1}H-NMR data of the compound 196 are as follows:

Melting point: 244-258 °C

^{1}H-NMR(DMSO-d_6) δ;

4.97 and 5.17(d,J = 12.7Hz,2H), 6.52(s,1H), 7.16-7.23(m,2H), 7.27-7.33(m,3H), 7.42-7.54(m,2H), 7.68 and 7.71(s,1H)

Example 121

7-(3-(S)-Aminopyrrolidin-1-yl)-6-fluoro-1-(1,2,4-triazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.197):

A mixture of compound No.194 (50mg) was dissolved in acetonitrile (5ml), to which triethylamine (21mg) and 3-(S)-aminopyrrolidine (21mg) were added and stirred at 80 °C for 30 minutes. The precipitate was filtrated and washed with ethanol. The title compound No. 197 was obtained as a yellow solid (46mg).

Melting point: 250-260 °C, colored from approx. 245 °C

^{1}H-NMR(DMSO-d_6) δ;

1.65-1.82(m,1H), 1.98-2.12(m,1H), 3.51-3.77(m,4H), 6.60(d,J = 7.8Hz,1H), 8.88(d,J = 16.1Hz,1H), 8.94-(s,1H), 9.22(s,1H)

Example 122

Ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-3-(1-methyl-1,2,4-triazol-5-ylamino)acrylate (Compound No.198):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (3.00g), ethyl orthoformate (2.38g) and acetic anhydride (3.85g) was stirred at 130 °C for 2 hours. After the excessive acetic anhydride and ethyl orthoformate were removed in vacuo, the residue was dissolved in chloroform (50ml). A solution of 5-amino-1-methyl-1,2,4-triazole (1.05g) in chloroform (30ml) was added thereto. The mixture was stirred at room temperature overnight. The solvent was removed. The residue was purified with a silicagel column (chloroform/ethyl acetate 5:1 as an eluent). The title compound No. 198 was obtained as a yellow solid (2.34g).

Melting point: 102-103 °C

^{1}H-NMR($CDCl_3$) δ;

1.20 and 1.26(t,J = 7Hz,3H), 3.86 and 3.91(s,3H), 4.06-4.23(m,2H), 7.42 and 7.56(d,J = 7Hz,1H), 7.72 and 7.76(s,1H), 8.85 and 8.97(d,J = 12.2Hz,1H)

Example 123

Ethyl 7-chloro-6-fluoro-1-(1-methyl-1,2,4-triazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.199):

A solution of compound No.198 (1.00g) and potassium carbonate (0.39g) in dimethylformamide (20ml) was stirred for 30 minutes at 90 °C. The solvent was removed and a 5% citric acid solution (50ml) and chloroform (50ml) were added thereto. The organic phase was dehydrated with Glauber's salt, followed by evaporation of solvent. The residue was suspended in a small amount of ethyl acetate for filtration. The title compound No. 199 was obtained as a colorless solid (0.79g).

Melting point: 256-263 °C

^{1}H-NMR($CDCl_3$) δ;

1.39(t,J = 7Hz,3H), 3.80(s,3H), 4.40(q,J = 7Hz,2H), 8.04(s,1H), 8.48(d,J = 7.3Hz,1H), 8.62(s,1H)

Example 124

7-Chloro-6-fluoro-1-(1-methyl-1,2,4-triazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.200):

Compound No.199 (0.1g) was dissolved in acetic acid (10ml) and 6N-HCl (3ml). The solution was stirred at 110 °C for 1 hour. After evaporation of the solvent, the residue was suspended in diethylether for filtration. The title compound No. 200 was obtained as a colorless solid (80mg).

Melting point: 238-242 °C

^{1}H-NMR(DMSO-d_6) δ;

3.71(s,3H), 8.22(s,1H), 8.75(d,J = 7.8Hz,1H), 9.06(s,1H)

Example 125

7-(3-(S)-Aminopyrrolidin-1-yl)-6-fluoro-1-(1-methyl-1,2,4-triazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrochloride (Compound No.201):

A mixture of compound No.200 (50mg), triethylamine (40mg) and 3-(S)-aminopyrrolidine (24mg) in acetonitrile (5ml) was stirred at 80 °C for 60 minutes. The precipitate was filtrated and washed with ethanol, and was dissolved in 6N-HCl to obtain a hydrochloride. The solvent was removed and suspended in diethylether for filtration. The title compound No. 201 was obtained as a pale brown solid (47mg).

Melting point: Colored from approx. 240 °C, 265-275 °C decomposed

^{1}H-NMR(DMSO-d_6) δ;

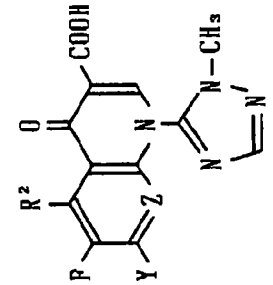
2.13(brs,1H), 2.20(brs,1H), 3.72(s,3H), 8.14(d,J = 12.2Hz,1H), 8.20(s,1H), 8.35(brs,3H), 8.88(s,1H)

Example 126

Compounds Nos. 202 and 203 listed in Table 42 were synthesized in a similar manner to Example 125.

Table 4 2

Compound :



Compound No.	R²	Y	Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
202	H	(3S, 4S) · HCl	N	Pale yellow solid	270 or more	[DMSO-d_6] δ : 1.06(d, J=6.4Hz, 3H), 2.40-2.70(brs, 1H), 3.72(s, 3H), 8.13(d, J=12.7Hz, 1H), 8.19(s, 1H), 8.86(s, 1H)	Et_3N/CH_3CN → AcOH, HClaq
203	H	· HCl	N	Pale yellow solid	270 or more	[DMSO-d_6] δ : 3.17(brs, 4H), 3.70(s, 4H), 3.72(s, 3H), 8.21(s, 1H), 8.27(d, J=13.2Hz, 1H), 8.97(s, 1H)	〃

Example 127

Ethyl 2-(2,4,5-trifluorobenzoyl)-3-(1-methyl-1,2,4-triazol-5-ylamino)acrylate (Compound No.204):

A mixture of ethyl 2,4,5-trifluorobenzoylacetate (1.50g), ethyl orthoformate (2.24g) and acetic anhydride (1.09g) was stirred at 130 °C for 3 hours. After the excessive acetic anhydride and ethyl orthoformate were removed in vacuo, a solution of 5-amino-1-methyl-1,2,4-triazole (0.48g) in benzene (30ml) and methanol (15ml) was added to the residue. The mixture was stirred at room temperature overnight. The solvent was removed. The residue was purified with a silicagel column (chloroform as an eluent). The title compound No. 204 was obtained as a yellow oil (0.43g).

^{1}H-NMR($CDCl_3$) δ;

1.05 and 1.21(t,J = 7Hz,3H), 3.83 and 3.88(s,3H), 4.10-4.22(m,2H), 6.87-6.97(m,1H), 7.29-7.37 and 7.47-7.37(m,1H), 7.68 and 7.72(s,1H), 8.57 and 8.84(d,J = 12Hz,1H)

Example 128

Ethyl 6,7-difluoro-1-(1-methyl-1,2,4-triazol-5-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.205):

A solution of compound No.204 (347mg) and potassium carbonate (148mg) in dimethylformamide (8ml) was stirred for 30 minutes at 90 °C. The solution was removed. An aqueous 5% citric acid (25ml) and chloroform (25ml) were used for separation. The organic phase was dried over Na_2SO_4, followed by evaporation. A small amount of ethyl acetate was added to the residue and the precipitate was filtrated. The title compound No. 205 was obtained as a colorless solid (0.235g).

Melting point: 230-231 °C

^{1}H-NMR($CDCl_3$) δ;

1.40(t,J = 7Hz,3H), 3.81(s,3H), 4.40(q,J = 7Hz,2H), 6.67(dd,J = 6Hz,J = 10Hz,1H), 8.13(s,1H), 8.29-(dd,J = 8.3Hz,J = 9.8Hz,1H), 8.39(s,1H)

Example 129

6,7-Difluoro-1-(1-methyl-1,2,4-triazol-5-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.206):

Compound No.205 (0.2g) was dissolved in acetic acid (10ml) and 6N-HCl (3ml). The solution was stirred at 110 °C for 1 hour. After evaporation of the solvent, the residue was suspended in diethylether for filtration. The title compound No. 206 was obtained as colorless solid (166mg).

Melting point: 254-264 °C

^{1}H-NMR(DMSO-d_6) δ;

3.76(s,3H), 7.37(dd,J = 6.3Hz,J = 11.2Hz,1H), 8.28(s,1H), 8.34(dd,J = 8.3Hz,J = 10.3Hz,1H), 9.16(s,1H)

Example 130

7-(3-(S)-Aminopyrrolidin-1-yl)-6-fluoro-1-(1-methyl-1,2,4-triazol-5-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hydrochloride (Compound No.207):

A mixture of compound No.206 (50mg), triethylamine (39mg) and 3-(S)-aminopyrrolidine (22mg) in acetonitrile (5ml) was stirred at 80 °C for 60 minutes. The precipitate was filtrated and washed with ethanol, then dissolved in 6N-HCl to obtain a hydrochloride. The solvent was removed and suspended in diethylether for filtration. The title compound No. 207 was obtained as a pale yellow solid (59mg).

Melting point: Colored from approx. 257 °C, 262-266 °C decomposed

^{1}H-NMR(DMSO-d_5) δ;

2.01-2.16(brs,1H), 2.16-2.28(brs,1H), 3.40-3.52(brs,1H), 3.52-3.67(brs,2H), 3.75(s,3H), 3.82-3.93(brs,1H), 5.70(d,J = 7.3Hz,1H), 7.93 (d,J = 14.2Hz,1H), 8.32(s,1H), 9.00(s,1H)

Example 131

Ethyl 2-(2,4,5-trifluorobenzoyl)-3-(1,2,3-triazol-4-ylamino)acrylate (Compound No.208):

A mixture of ethyl 2,4,5-trifluorobenzoylacetate (2.00g), ethyl orthoformate (1.81g) and acetic anhydride (3.73g) was stirred at 130 °C for 3 hours. The excessive acetic acid and ethyl orthoformate were removed in vacuo, and the residue was dissolved in benzene (30ml), to which a solution of 4-amino-1,2,3-triazole (0.68g) in methanol (20ml) was added. The mixture was stirred at room temperature overnight. The solvent was removed. The residue was purified with a silicagel column (chloroform/ethyl acetate 10:1 as an eluent). The title compound No. 208 was obtained as a yellow solid (1.93g).

Melting point: 157-159 °C

^{1}H-NMR($CDCl_3$) δ;

1.02 and 1.14(t,J = 7Hz,3H), 4.04-4.20(m,2H), 6.84-6.97(m,1H), 7.26-7.36 and 7.42-7.56(m,1H), 7.57 and 7.61(s,1H), 8.52 and 8.70(d,J = 13.2Hz,1H)

Example 132

Ethyl 6,7-difluoro-1-(1,2,3-triazol-4-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.209):

A solution of compound No.208 (300mg) and potassium carbonate (124mg) in dimethylformamide (6ml) was stirred for 30 minutes at 90 °C. The solvent was removed. The residue was suspended in water for filtration. The title compound No. 209 was obtained as a pale yellow solid (221mg).

Melting point: 298 °C

^{1}H-NMR(DMSO-d_6) δ;

1.27(t,J = 7Hz,3H), 4.23(B,J = 7Hz,2H), 7.36((dd,J = 6.8Hz, J = 11.7Hz,1H), 8.15-(dd,J = 8.8Hz,J = 10.7Hz,1H), 8.51(s,1H), 8.59(s,1H)

Example 133

6,7-Difluoro-1-(1,2,3-triazol-4-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.210):

Compound No.209 (0.1g) was dissolved in tetrahydrofuran (10ml) and 6N-HCl (3ml). The solution was refluxed with heating for 1 hour. After evaporation of the solvent, the residue was suspended in diethylether for filtration. The title compound No. 210 was obtained as a pale yellow solid (82mg).

Melting point: 215-224 °C

^{1}H-NMR(DMSO-d_6) δ;

7.58(dd,J = 6.8Hz,J = 11.7Hz,1H), 8.34(dd,J = 8.3Hz, J = 10.3Hz,1H), 8.45-8.59(brs,1H), 8.88(s,1H)

Example 134

7-(3-(S)-Aminopyrrolidin-1-yl)-6-fluoro-1-(1,2,3-triazol-4-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.211):

A mixture of compound No.210 (50mg), triethylamine (38mg) and 3-(S)-aminopyrrolidine (27mg) in acetonitrile (5ml) was stirred at 80 °C for 30 minutes. The precipitate was filtrated and washed with ethanol. The title compound No. 211 was obtained as a pale brown solid (47mg).

Melting point: 300 °C

^{1}H-NMR(DMSO-d_6) δ;

1.57-1.69(brs,1H), 1.69-1.83(brs,1H), 6.54(d,J = 7.8Hz,1H), 7.73(s,1H), 7.83(d,J = 14.2Hz,1H), 8.51(s,1H)

Example 135

Ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-3-(1-methyl-1,2,3-triazol-5-ylamino)acrylate (Compound No.212):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (2.80g), ethyl orthoformate (2.22g) and acetic anhydride (3.57g) was stirred at 130 °C for 1.5 hours. After the excessive acetic acid and ethyl orthoformate were removed, the residue was dissolved in chloroform (50ml). A solution of 5-amino-1-methyl-1,2,3-triazole (98ml) in methanol (60ml) was added thereto. The mixture was stirred at room temperature for 0.5 hour.

The solvent was removed and then purified through a silicagel column (chloroform/methanol 40:1 as an eluent). The solidified substance was suspended in n-hexane for filtration. The title compound No. 212 was obtained as a colorless solid (2.94g).

Melting point: 187-189 °C

^{1}H-NMR($CDCl_3$) δ; 0.96 and 1.12(t,J = 7Hz,3H), 4.05-4.25(m,2H), 4.10(s,3H), 7.43(d,J = 6.8Hz), 7.74-(s,1H), 8.32 and 8.36(s,1H)

Example 136

Ethyl 6-fluoro-7-chloro-1-(1-methyl-1,2,3-triazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.213):

A solution of compound No.212 (300mg) and potassium carbonate (107mg) in dimethylformamide (6ml) was stirred for 30 minutes at 90 °C. The solvent was removed. An aqueous 5% citric acid (25ml) and chloroform (100ml) were used for separation. The organic phase was dried over Na_2SO_4 and the solvent was removed. The residue was suspended in diethylether for filtration. The title compound No. 213 was obtained as a colorless solid (249mg).

Melting point: 251 °C decomposed

^{1}H-NMR($CDCl_3$) δ;

1.40(t,J = 7Hz,3H), 3.95(s,3H), 4.41(q,J = 7Hz,2H), 7.89(s,1H), 8.46(s,1H), 8.49(d,J = 6.8Hz,1H)

Example 137

6-Fluoro-7-chloro-1-(1-methyl-1,2,3-triazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.214):

Compound No.213 (1.51g) was dissolved in acetic acid (70ml) and 6N-HCl (20ml). The solution was stirred at 110 °C for 1 hour. After evaporation of the solvent, the residue was suspended in diethylether for filtration to obtain the title compound No. 214 as a pale yellow solid (1.33g).

Melting point: 240-245 °C

^{1}H-NMR(DMSO-d_6) δ;

3.87(s,3H), 8.12(s,1H), 8.78(d,J = 8.3Hz,1H), 9.00(s,1H)

Example 138

7-(3-(S)-Aminopyrrolidin-1-yl)-6-fluoro-1-(1-methyl-1,2,3-triazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrochloride (Compound No.215):

A mixture of compound No.214 (50mg), triethylamine (36mg) and 3-(S)-aminopyrrolidine (19mg) in acetonitrile (5ml) was stirred at 80 °C for 60 minutes. After the precipitate was collected by filtration, it was washed with ethanol, then dissolved in 6N-HCl to obtain a hydrochloride. After the solvent was removed, the residue was suspended in diethylether for filtration. The title compound No. 215 was obtained as a pale orange solid (37mg).

Melting point: 269 °C decomposed

^{1}H-NMR(DMSO-d_6) δ;

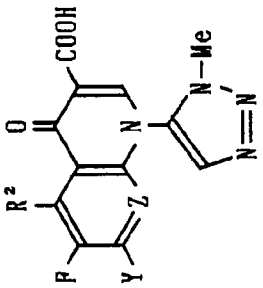
1.92-2.13(brs,1H), 2.13-2.30(brs,1H), 3.88(s,3H), 8.09(s,1H), 8.14(d,J = 12.2Hz,1H), 8.28(brs,3H), 8.78-(s,1H)

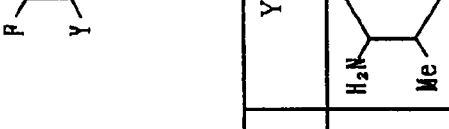
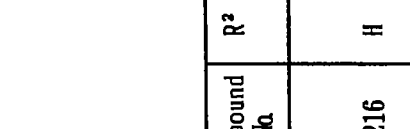
Example 139

Compound Nos. 216-217 listed in Table 43 were synthesized in a similar manner to Example 138.

Table 43

Compound:



Compound No.	R^2	Y	Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
216	H	 (3S, 4S) · HCl	N	Pale yellow solid	Decomposed from 255	[DMSO-d_6] δ : 1.05(d, J=6Hz, 3H), 2.42-2.67(brs, 1H), 3.88(s, 3H), 8.09(s, 1H), 8.14(d, J=12.7Hz, 1H), 8.21(brs, 3H), 8.78(s, 1H)	Et_3N/CH_3CN
217	H	 · HCl	N	Pale yellow solid	Decomposed from 275	[DMSO-d_6] δ : 3.31(brs, 4H), 3.90(brs, 4H), 3.93(s, 3H), 8.07-8.14(brs, 1H), 8.17(d, J=13.2Hz, 1H), 8.88(s, 1H)	〃

Example 140

Ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-3-(1-methyltetrazol-5-ylamino)acrylate (Compound No.218):

A mixture of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (1.04g), ethyl orthoformate (1.12g) and acetic anhydride (1.80g) was stirred at 130 °C for 2 hours. The excessive acetic anhydride and ethyl orthoformate were removed, and dissolved in chloroform (30 ml), to which a solution of 5-amino-1-methyltetrazole in methanol was added. The mixture was stirred at room temperature for 3 days. The solvent was removed. The residue was purified through a silicagel column (chloroform/ethyl acetate 10:1 as an eluent). The title compound No. 218 was obtained as a red-brown oil (516mg).

^{1}H-NMR($CDCl_3$) δ;

0.99 and 1.22(t,7Hz,3H), 4.01-4.24(m,2H), 4.05 and 4.10(s,3H), 7.34 and 7.44(d,J = 7.0Hz,1H), 8.81 and 8.99(d,J = 12Hz,1H)

Example 141

Ethyl 6-fluoro-7-chloro-1-(1-methyltetrazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No.219):

To a solution of compound No.218 (0.08g) in tetrahydrofuran (8ml), 11mg of sodium hydride was added. Then the solution was stirred for 2 days at room temperature. After addition of 5% citric acid solution for neutralization, the solvent was removed. A citric acid solution and chloroform were used for separation. The organic phase was dried over Na_2SO_4 and the solvent was removed. The residue was purified through a silicagel column (chloroform:ethyl acetate = 1:1). The title compound No. 219 was obtained as a pale yellow solid (21mg).

Melting point: 210-215 °C

^{1}H-NMR($CDCl_3$) δ;

1.40(t,J = 7Hz,3H), 4.06(s,3H), 4.41(q,J = 7Hz,2H), 8.51(d,J = 6.8Hz,1H), 8.65(s,1H)

Example 142

6-Fluoro-7-chloro-1-(1-methyltetrazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.220):

Compound No.219 (123mg) was dissolved in acetic acid (5ml) and 6N-HCl (5ml). The solution was stirred at 110 °C for 2 hours. After evaporation of the solvent, the residue was submitted to a constant boiling with toluene. The residue was suspended in diethylether for filtration. The title compound No. 220 was obtained as a pale brown solid (101mg).

Melting point: 213-220 °C

^{1}H-NMR(DMSO-d_6) δ;

3.97(s,1H), 8.77(d,J = 7.8Hz,1H), 9.09(s,1H)

Example 143

7-(3-(S)-Aminopyrrolidin-1-yl)-6-fluoro-1-(1-methyltetrazol-5-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrochloride (Compound No.221):

A mixture of compound No.220 (45mg), triethylamine (37mg) and 3-(S)-aminopyrrolidine (13mg) in acetonitrile (5ml) was stirred at room temperature for 5 minutes. The precipitate was filtrated, washed with ethanol, and dissolved in 6N-HCl to obtain a hydrochloride. After the solvent was removed, the residue was suspended in diethylether for filtration. The title compound No. 221 was obtained as a pale yellow solid (38mg).

Melting point: 258 °C decomposed

^{1}H-NMR(DMSO-d_6) δ;

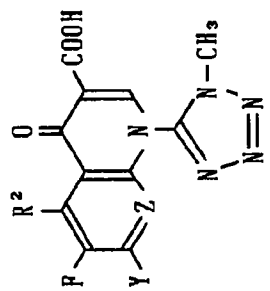
1.96-2.15(brs,1H), 2.15-2.31(brs,1H), 3.87(brs, 2H), 3.94(s,1H), 3.99(s,3H), 8.15(d,J = 12.7Hz,1H), 8.30-(brs,3H), 8.95(s,1H)

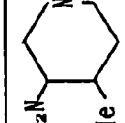
Example 144

Compound No. 222 listed in Table 44 was synthesized in a similar manner to Example 143.

Table 44

Compound:



Compound No.	R^2	Y	Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
222	H	 (3S, 4S) · HCl	N	Pale brown solid	Decomposed from 248	[DMSO-d_6] δ : 2.42-2.65(br, 1H), 3.76(brs, 2H), 3.94(s, 1H), 3.99(s, 3H), 8.15(d, J=12.7Hz, 1H), 8.29(brs, 3H), 8.94(s, 1H)	Et_3N/CH_3CN ↓ AcOH, HClaq

Example 145

Ethyl 2-(2-methyl-3,4,6-trifluorobenzoyl)-3-(4-methyl-1,2,5-oxadiazol-3-ylamino)acrylate (Compound No.223):

A mixture of ethyl 2-methyl-3,4,6-trifluorobenzoylacetate (2.6g), ethyl orthoformate (2.5ml) and acetic anhydride (2.8ml) was stirred at 130 °C for 2 hours. After the solvent was removed in vacuo, a solution of 3-amino-4-methyl-1,2,5-oxadiazole (0.99g) in chloroform(20ml) was added to the residue. The mixture was stirred at room temperature for 24 hours. The solvent was removed. The residue was purified by chromatography on silicagel (chloroform as an eluent). The title compound No. 223 was obtained as a yellow oil (3.4g).

^{1}H-NMR($CDCl_3$) δ;

1.01 and 1.16(t,J = 7Hz,3H), 2.22 and 2.28(d,J = 2.2Hz,3H), 2.46 and 2.51(s,3H), 4.05-4.2(m,2H), 6.7-6.9-(m,1H), 8.62 and 8.79(d,J = 12.6Hz,1H)

Example 146

Ethyl 5-methyl-6,7-difluoro-1-(4-methyl-1,2,5-oxadiazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.224):

To a solution of compound No.223 (3.4g) in tetrahydrofuran (50ml), 0.37g of sodium hydride (60% in oil) was added. Then the solution was stirred for 7 hours at 70 °C. After the solvent was removed and a 5% citric acid solution (10ml) was added thereto, extraction was carried out with chloroform (100ml), followed by drying over $MgSO_4$ and evaporation. To the residue was added isopropylether, and the precipitate was filtrated. The title compound No. 224 was obtained as a yellow solid (1.68g).

Melting point: 173.5-174.0 °C

^{1}H-NMR($CDCl_3$) δ;

1.39(t,J = 7Hz,3H), 2.35(s,3H), 2.91(d,J = 2.6Hz,3H), 4.39(q,J = 7Hz,2H), 6.49(dd,J = 6Hz,J = 11Hz,1H), 8.25(s,1H)

Example 147

5-Methyl-6,7-difluoro-1-(4-methyl-1,2,5-oxadiazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.225):

Compound No.224 (1.68g) was dissolved in acetic acid (20ml) and 6N-HCl (6ml). The solution was stirred at 110 °C for 50 minutes. After cooling, ice (50ml) was added thereto, and the precipitate was filtrated, followed by washing with water, ethanol and isopropyl ether. The title compound No. 225 was obtained as a yellow solid (1.43g).

Melting point: 199.5-202 °C

^{1}H-NMR(DMSO-d_6) δ;

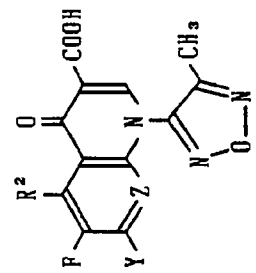
2.29(s,3H), 2.85(d,J = 2.5Hz,3H), 7.51(dd,J = 6.8Hz, J = 11.1Hz,1H), 9.08(s,1H)

Example 148

Compounds Nos. 226-229 listed in Table 45 were synthesized in a similar manner to Example 117, proceeding from the compound No.225.

Table 45

Compound:



Compound No.	R²	Y	Z	Property	Melting point (°C)	¹H-NMR	Solvent
226	Me	(S) H₂N, N, ·HCl	C—H	Pale yellow solid	Decomposed from 266	[DMSO-d₆] δ : 2.0-2.4(m, 2H), 2.33(s, 3H), 2.77(s, 3H), 3.4-3.9(m, 5H), 5.73(d, J=7.7Hz, 1H), 8.36(brs, 3H), 8.89(s, 1H)	Et₃N/CH₃CN → AcOH, HClaq
227	Me	H₂N, Me (3S, 4S) N, ·HCl	C—H	Pale yellow solid	241-245	[DMSO-d₆] δ : 1.08(d, J=6.5Hz, 3H), 2.33(s, 3H), 2.4-2.6(m, 1H), 2.76(s, 3H), 3.5-4.9(m, 5H), 5.70(d, J=6Hz, 1H), 8.37(brs, 3H), 8.89(s, 1H)	〃
228	Me	HN, N, ·HCl	C—H	Colorless solid	Decomposed from 273	[DMSO-d₆] δ : 2.31(s, 3H), 2.79(s, 3H), 3.22(s, 4H), 3.4(s, 4H), 6.38(d, J=7.7Hz, 1H), 8.98(s, 1H), 9.42(brs, 2H)	〃
229	Me	H₂N, N	C—H	Colorless solid	241— 242.5	[DMSO-d₆] δ : 2.29(s, 3H), 2.69(d, J=3Hz, 3H), 3.6-3.85(m, 3H), 4.24(brs, 2H), 5.53(d, J=8.1Hz, 1H), 8.82(s, 1H)	Et₃N CH₃CN

Example 149

Ethyl 2-(2,3,4,5-tetrafluorobenzoyl)-3-(4-methyl-1,2,5-oxadiazol-3-ylamino)acrylate (Compound No.230):

A mixture of ethyl 2,3,4,5-tetrafluorobenzoylacetate (1.06g), ethyl orthoformate (1.2ml) and acetic anhydride (1.3ml) was stirred at 130°C for 5 hours. After the solvent was removed in vacuo, a solution of 3-amino-4-methyl-1,2,5-oxadiazole (0.4g) and triethylamine (0.4g) in chloroform (10ml) was added to the residue. The mixture was stirred at room temperature for 1 hour. The solvent was removed. The residue

was purified by chromatography on silicagel (chloroform/ethyl acetate 10:1 as an eluent). The title compound No. 230 was obtained as a pale yellow solid (1.17g).

Melting point: 88-92 °C

^{1}H-NMR($CDCl_3$) δ;

1.07 and 1.24(t,J = 7Hz,3H), 2.46 and 2.49(s,3H), 4.1-4.3(m,2H), 7.1-7.4(m,1H), 8.47 and 8.73 (d,J = 12.6Hz,1H)

Example 150

Ethyl 6,7,8-trifluoro-1-(4-methyl-1,2,5-oxadiazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No.231):

To a solution of compound No.230 (1.2g) in tetrahydrofuran (50ml), 0.128g of sodium hydride (60% in oil) was added. Then the solution was stirred for 1 hour at 50 °C. After addition of 5% citric acid solution (10ml), tetrahydrofuran was removed in vacuo. The precipitate was filtrated and washed with water, ethanol and ether. The title compound No. 231 was obtained as a colorless solid (0.92g).

Melting point: 201-202 °C

^{1}H-NMR($CDCl_3$) δ;

1.4(t,J = 7Hz,3H), 2.4(s,3H), 4.4(q,J = 7Hz,2H), 8.15-8.25(m,1H), 8.29(s,1H)

Example 151

6,7,8-Trifluoro-1-(4-methyl-1,2,5-oxadiazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.232):

Compound No.231 (0.8g) was dissolved in acetic acid (10ml) and c-HCl (4ml). The solution was stirred at 110 °C for 2 hours. After cooling, 50ml of water was added, and the precipitate was filtrated and washed with water, ethanol and ether. The title compound No. 232 was obtained as a colorless solid (0.6g).

Melting point: 204.5-205 °C

^{1}H-NMR(DMSO-d_6) δ;

2.4(s,3H), 8.2-8.3(m,1H), 9.08(s,1H)

Example 152

6,8-Difluoro-7-(3-(S)-aminopyrrolidin-1-yl)-1-(4-methyl-1,2,5-oxadiazol-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.233):

A mixture of compound No.232 (100mg),triethylamine 63mg) and 3-(S)-aminopyrrolidine(40mg) in acetonitrile (3ml) was stirred at 80 °C for 3 minutes. After cooling, the precipitate was filtrated. The title compound No. 233 was obtained as a yellow solid (60mg).

Melting point: 169-170 °C

^{1}H-NMR(DMS)-d_6 + CF_3COO-d) δ;

1.99 and 2.17(brs,2H), 2.37(s,3H), 3.87(brs,3H), 7.86(d,J = 13.7Hz,1H), 8.11(brs,3H), 8.92(s,1H)

Example 153

Compounds Nos. 234-239 listed in Tables 46 and 47 were synthesized in a similar manner to Example 4, proceeding from the compound No.3.

Example 154

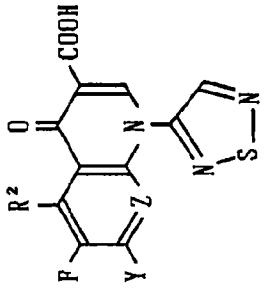
Compounds Nos. 240-243 listed in Table 48 were prepared in a similar manner to Example 11, proceeding from the compound No.159.

Example 155

Compounds Nos. 244 and 245 listed in Table 49 were prepared in a similar manner to Example 41, proceeding from the compound No.79.

Table 46

Compound:



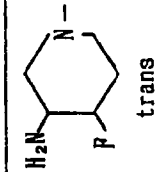
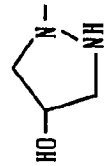
Compound No.	R^2	Y	Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
234	H	 trans	N	Dim yellow solid	Decomposed from 251	[DMSO-d_6] δ : 3.05-4.2(m,5H), 5.29と5.48(brs,合して1H), 8.17(d,J=12.4Hz,1H), 9.01(s,1H), 9.38(s,1H)	Et_3N CH_3CN
235	H		N	Pale yellow solid	244-246	[DMSO-d_6] δ : 2.45-2.55(m,4H), 3.9-4.0(m,4H), 8.21(d,J=13.2Hz,1H), 9.02(s,1H), 9.31(s,1H)	〃
236	H		N	Brown solid	Decomposed from 172	[DMSO-d_6] δ : 2.98(s,2H), 3.74(brs,1H), 4.48(s,1H), 5.9-6.2(m,1H), 7.96(d,J=12.2Hz,1H), 8.76(s,1H), 9.49(s,1H)	〃

Table 47

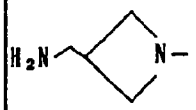
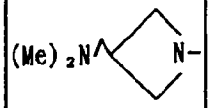
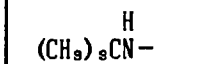
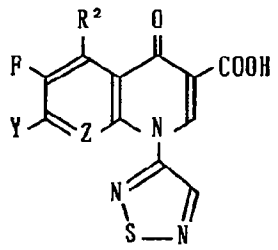
Compound No.	R^2	Y	Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
237	H		N	Yellow solid	Decomposed from 280	[DMSO-d_6+重トリフルオロ酢酸] δ ; 2.9-3.2(m, 3H), 3.7-4.4(m, 4H), 8.04(d, J=11.1Hz, 1H), 8.99(s, 1H), 9.31(s, 1H)	Et_3N CH_3CN
238	H		N	Pale yellow solid	217-220	[DMSO-d_6] δ ; 2.20(s, 6H), 2.4-2.7(m, 2H), 2.97(brs, 1H), 3.4-4.6(m, 4H), 8.0(d, J=11.1Hz, 1H), 8.97(s, 1H), 9.31(s, 1H)	〃
239	H		N	Red solid	251-254	[$CDCl_3$] δ ; 1.3(s, 9H), 5.51(brs, 1H), 8.04(d, J=10.7Hz, 1H), 8.86(s, 1H), 8.89(s, 1H)	〃

Table 48

Compound:



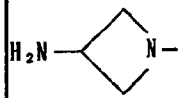
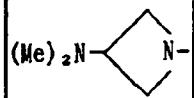
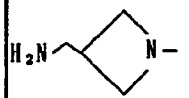
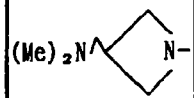
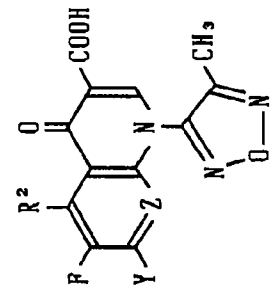
Compound No.	R^2	Y	Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
240	Me	 · HCl	C H	Pale yellow solid	257-259	[DMSO-d_6] δ ; 2.7(s, 3H), 3.67(brs, 2H) 3.8(brs, 1H), 4.21(brs, 2H), 5.79(d, J=6.8Hz, 1H), 8.81(s, 1H), 9.22(s, 1H)	Et_3N/CH_3CN ↓ AcOH, HClaq
241	Me	 · HCl	C H	Colorless solid	242— 244.5	[DMSO-d_6] δ ; 2.71(s, 6H), 2.75(d, J=2.5Hz, 3H), 4.1-4.5(m, 5H), 5.98(d, J=7.7Hz, 1H), 8.86(s, 1H), 9.25(s, 1H)	〃
242	Me		C H	Pale yellow solid	Decomposed from 231	[DMSO-d_6] δ ; 2.7(s, 3H), 2.55-2.85(br, 3H), 3.78(brs, 2H), 4.06(brs, 2H), 5.77(d, J=8.1Hz, 1H), 8.78(s, 1H), 9.24(s, 1H)	Et_3N CH_3CN
243	Me		C H	Pale yellow solid	221— 224.5	[DMSO-d_6] δ ; 2.11(s, 6H), 2.4-2.6(m, 2H), 2.71(s, 3H), 2.75-2.9(br, 1H), 3.7(brs, 2H), 4.12(brs, 2H), 5.81(d, J=8.1Hz, 1H), 8.8(s, 1H), 9.23(s, 1H)	〃

Table 49

Compound:



Compound No.	R²	Y	Z	Property	Melting point (℃)	¹H-NMR	Solvent
244	H	· HCl	N	Pale yellow solid	279–280.5	[DMSO-d_6] δ : 1.45-1.7(m, 2H), 2.0-2.15(m, 2H), 2.31(s, 3H), 3.05-3.25(m, 2H), 4.1-4.25(m, 2H), 8.17(d, J=13.7Hz, 1H), 8.36(brs, 3H) 8.96(s, 1H)	Et_3N/CH_3CN → AcOH, HClaq
245	H		N	Colorless solid	244-245	[DMSO-d_6] δ : 2.32(s, 3H), 3.8-4.7(m, 3H), 8.04(d, J=11.1Hz, 1H), 8.86(s, 1H)	Et_3N CH_3CN

Example 156

7-{3-(S)-(2-(S)-t-Buthoxycarbonylaminopropionyl) aminopyrrolidin-1-yl}-6-fluoro-1-(4-methyl-1,2,5-oxadiazol-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Compound No.246):

A solution of Boc-L-alanine (190mg), 1-hydroxybenzotriazole (153mg), WSC hydrochloride (192mg) and triethylamine (101mg) in chloroform (10mg) was stirred at room temperature for 0.5 hour. To this solution was added a solution of compound No.81 (370mg) in DMF (10ml), then stirred at 50 °C for 1 day. After evaporation of the solvent, an aqueous 5% citric acid solution (20ml) was added, then extracted with chloroform (100ml). The organic phase was dried ($MgSO_4$) and removed. After addition of isopropylether for solidification, the precipitate was filtrated. The title compound No. 246 was obtained as a yellow solid.

Melting point: 205.5-207.5 °C

^{1}H-NMR($CDCl_3$) δ;

1.33(d,J = 6.8Hz,3H), 1.40(s,9H), 2.2(brs,2H), 2.35 (s,3H), 4.1(brs,1H), 4.55(brs,1H), 5.03(brs,1H), 7.0-7.2-(br,1H), 8.0(d,J = 12Hz,1H), 8.57(s,1H)

Example 157

7-{3-(S)-(2-(S)-Aminopropionyl)aminopyrrolidin-1-yl}-6-fluoro-1-(4-methyl-1,2,5-oxadiazol-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrochloride (Compound No.247):

〈Method a〉

Compound No.246 (90mg) was dissolved in chloroform (10ml) and 4N-HCl/dioxane (1ml). The solution was stirred at room temperature for 20 minutes. After evaporation of the solvent, ether was added. The precipitate was filtrated. The title compound No. 247 was obtained as a yellow solid (80mg).

〈Method b〉

Compound No.78 (2.1g) synthesized in Example 39 and 3-(S)-aminopyrrolidine (0.86g) was dissolved in chloroform (50ml). The solution was stirred at room temperature for 10 hours. After evaporation of the solvent, ether was added to obtain a red solid (2.4g).

To a solution of Boc-L-alanine (945mg) and N-methylmorpholine (505mg) in dichloromethane (20ml), 0.65ml of isobutylchloroformate was added with ice cooling. Then the solution was stirred for 20 minutes. To this solution was added the red solid (2.01g) obtained above, then stirred at room temperature for 30 minutes. The reaction solution was washed with aqueous 5% citric acid, aqueous 5% $NaHCO_3$ and water successively. The organic phase was dried ($MgSO_4$) and evaporated. To the residue was added ether (20ml). The precipitate was filtrated to obtain a pale red solid (2.5g).

This compound is an ethyl ester derivative of compound No.244.

Melting point: 107-113 °C

^{1}H-NMR($CDCl_3$) δ;

1.2-1.5(m,15H), 1.95-2.2(br,2H), 2.22(s,3H), 3.7-4.0(br,1H), 4.2-4.3(m,3H), 4.55-4.8(br,1H), 7.64-(d,J = 12Hz,1H), 8.41(s,1H)

This red solid (1.5g) was dissolved in tetrahydrofuran (30ml) and 6N-HCl (5ml). The solution was stirred at room temperature for 48 hours. After evaporation of the solvent, ethanol was added to the residue. The precipitate was filtrated. The title compound No. 247 was obtained as a yellow solid (0.98g).

Melting point: 223.0-225.0 °C

^{1}H-NMR(DMSO-d_6) δ;

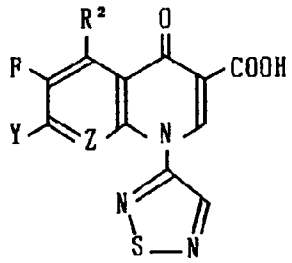
1.32(d,J = 6.8Hz,3H), 1.8-2.2(m,2H), 2.33(s,3H), 3.2-4.2(m,4H), 4.35(brs,1H), 8.08(d,J = 12.4Hz,1H), 8.26-(brs,3H), 8.90(s,1H), 9.0(d,1H)

Example 158

Compound Nos. 248-252 listed in Tables 50 and 51 were synthesized in a similar manner to Example 11, proceeding from the compound No.3.

Table 5 0

Compound :



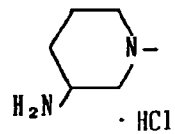
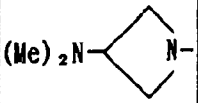
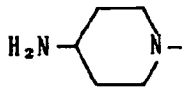
Compound No.	R^2	Y	Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
248	H	 · HCl	N	Pale yellow solid	258.5— 259.5	[DMSO-d_6] δ ; 1.5-1.85(m, 3H), 1.99(brs, 1H), 3.2-3.55(m, 3H), 3.7-3.85(m, 1H), 4.05-4.2(m, 1H), 8.21(d, J=12.8Hz, 1H), 8.38(brs, 3H), 9.01(s, 1H), 9.33(s, 1H)	Et_3N/CH_3CN ↓ AcOH, HClaq
249	H	 · HCl	N	Colorless solid	Decomposed from 272	[DMSO-d_6] δ ; 2.77(s, 6H), 4.2-4.8(m, 5H), 8.19(d, J=11.5Hz, 1H), 9.03(s, 1H), 9.33(s, 1H)	〃
250	H	 · HCl	N	Pale yellow solid	247-250	[DMSO-d_6] δ ; 1.45-1.68(m, 2H), 1.9-2.1(m, 2H), 3.07-3.25(m, 2H), 4.1-4.3(m, 2H), 8.2(d, J=13Hz, 1H), 8.18(brs, 3H), 9.02(s, 1H), 9.28(s, 1H)	〃

Table 5 1

Compound No.	R^2	Y	Z	Property	Melting point (℃)	^{1}H-NMR	Solvent
251	H		N — N	Colorless powder	214-216 (Decomposed)	[DMSO-d_6] δ : 1.60-1.85(m,5H), 3.15-3.22(m,1H), 3.51-4.15(m,6H), 8.17(d,J=12.8Hz,1H), 9.02(s,1H), 9.30(brs,1H)	Et_3N/CH_3CN ↓ AcOH, HClaq
252	H	(1S,6S)	N — N	Colorless powder	215-218 (Decomposed)	[DMSO-d_6] δ : 1.60-1.85(m,5H), 3.15-3.22(m,1H), 3.51-4.15(m,6H), 8.17(d,J=12.8Hz,1H), 9.02(s,1H), 9.30(brs,1H)	〃

Now, synthetic methods of 3-amino-4-methyl-1,2,5-thiadiazol are described as reference examples:

Reference Example 1

4-Methyl-1,2,5-thiadiazol-3-carboxylic acid (Compound A):

To a mixture of sulfur monochloride (220ml) and DMF (400ml) was added 75g of 2,3-diaminobutylic acid dihydrobromide with ice cooling, then stirred at room temperature for 2 hours. This solution was poured into water (3 liters), then extracted with ether (3Lx4). The ether was removed in vacuo. The residue was dissolved in 5% aqueous $NaHCO_3$ solution (200ml) and washed with 100ml of carbondisulfide. After the solution was acidified with c-HCl, it was extracted with ether (1.3Lx2). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The title compound (A) was obtained as a pale yellow solid (7.5g).

Melting point: 123-129 °C

^{1}H-NMR(DMSO-d_6) δ;

2.72(s,3H)

Reference Example 2

3-t-Buthoxycarbonylamino-4-methyl-1,2,5-thiadiazole (Compound B):

A solution of compound A (7.5g), triethylamine (5.8g) and diphenylphosphorylazide (15.7g) in 2-methyl-2-propanol (200ml) was stirred for 20 hours under reflux with heating. The solvent was removed. After addition of ethyl acetate (500ml), the solution was washed with water, 5% aqueous citric acid, and 5% aqueous $NaHCO_3$ successively, followed by drying ($MgSO_4$) and distilation. The residue was purified by column chromatography on silicagel(chloroform as an eluent). The title compound (B) was obtained as a colorless solid (10.4g).

Melting point: 124-128 °C

^{1}H-NMR($CDCl_3$) δ;

1.53(s,9H), 2.50(s,3H), 7.1(brs,1H)

Reference Example 3

3-Amino-4-methyl-1,2,5-thiadiazole, hydrochloride (Compound C):

Compound B (15.2g) was dissolved in ethanol (200ml) and c-HCl (35ml). The solution was stirred at 50 °C for 4 hours. After evaporation of the solvent, 100ml of chloroform was added. The precipitate was filtrated. The title compound was obtained as a yellow solid (7.7g).

Melting point: 121-124 °C

^{1}H-NMR(DMSO-d_6) δ;

2.31(s,3H), 7.55(brs,3H)

Example 159

Antibacterial activity, absorption and excretion of the compounds indicated in Examples were tested as follows.

(1) Antibacterial activity:

The minimum inhibitory concentration (MIC: microgram/ml) is measured by the standard method of Japan Society of Chemotherapy, (Chemotherapy, Volume 29, No.1, pp.76-79, 1981). The results are shown in Table 52 in which compound numbers are the same as those indicated in Examples.

Table 52

Compound No.	Minimum Inhibitory Concentration (micro-g/ml)		
	E.Coli NIH JC-2 (IFO * 12734)	S.aureus 209P (IFO 12732)	P. aeruginosa (IFO 3445)
18	<0.013	0.2	0.1
19	<0.013	0.1	0.39
58	0.05	1.56	0.39
81	0.05	0.1	0.2
126	3.13	0.39	3.13
162	0.013	0.1	0.2
187	0.05	0.2	0.39

* Institute of Fermentation , Osaka

(2) Absorption and excretion:

The absorption and excretion after oral administration of the compounds of the present invention were tested by measuring the recovery in urine and bile as follows.

(a) Recovery in urine:

To a group of three male JCL-SD rats (6 weeks old) fasted overnight, a subject compound was orally administered as prepared to be 20 mg/10ml/kg with 0.5% of methylcellulose solution. The sampling was carried out by collecting urine in 0 to 6 hours and 6 to 24 hours. The concentration of the subject compound in the urine was examined by a disk method by using Bacillus subtilis ATCC 6633 as a testing bacillus to obtain an excretion rate in urine for 24 hours.

(b) Recovery in bile:

A subject compound was prepared in the same manner as the recovery test in urine and was orally administered to the rats. The bile was collected by using a polyethylene tube inserted into the choledochus over 24 hours. The concentration of the subject compound in the bile sample was examined in the same manner as the recovery in urine to obtain an excretion rate in bile for 24 hours.

The results are shown in Table 53.

Table 53

Compound No.	Excretion Rate (24 hours, %)	
	In Urine	In Bile
18	20	2
19	80.6	4.4

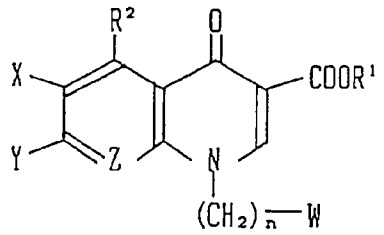
As described above, according to the present invention, the compounds represented by formula(1) and salts thereof, which are novel compounds, exhibit an extremely excellent antibacterial activity against gram-negative and gram-positive bacteria and possess a high oral absorbability.

Industrial Applicability

According to the present invention, the compounds represented by formula (1) and salts thereof are extremely valuable as antibacterial agents and very safe. Accordingly, they can be used as not only pharmaceuticals or medicines for the human body and animals but also medicines for fishes, agricultural chemicals and preservatives for foods. Further, the compounds of this invention are expected to have an anti viral action, especially an anti-HIV (human immuno deficiency virus) action, and therefore is considered to have preventive or curative activities against the AIDS.

Claims

1. A quinolone derivative represented by the formula (1), or a salt thereof:



(1)

wherein R^1 represents a hydrogen atom, or a carboxyl protective group, R^2 represents a hydrogen atom, halogen atom or a lower alkyl group, X represents a hydrogen atom or a halogen atom, Y represents a halogen atom, a cyclic amino group which may have a substituent, a cyclo- lower alkenyl group which may have a substituent, or a group R^3-$(CH_2)_m$-A- (wherein R^3 represents a hydrogen atom or an amino group which may have a substituent, A represents an oxygen atom or a sulfur atom and m represents a number of 0 to 3), Z represents a nitrogen atom or a group C-R^4 (wherein R^4 represents a hydrogen atom or a halogen atom), W represents a five-membered heterocyclic group which may have a substituent and which has 3 or more hetero-atoms, among which at least 2 hetero-atoms are nitrogen atoms, and n represents a number of 0 to 2.

2. A quinolone derivative or a salt thereof according to Claim 1, wherein said cyclic amino group represented by Y which may have a substituent is selected from the group consisting of saturated or unsaturated monocyclic 3 to 7 membered cyclic amino groups having one nitrogen atom, saturated or unsaturated monocyclic 3 to 7 membered cyclic amino groups having two nitrogen atoms, saturated or unsaturated monocyclic 3 to 7 membered cyclic amino groups having three or more nitrogen atoms, and saturated or unsaturated monocyclic 3 to 7 membered cyclic amino group having a hetero-atom selected from the group consisting of oxygen and sulfur.

3. A quinolone derivative or a salt thereof according to Claim 1, wherein said group represented by W is selected from the group consisting of thiadiazolyl group, triazolyl group, oxadiazolyl group and tetrazolyl group, each of which may have a substituent.

4. An antibacterial agent comprising the quinolone derivative or a salt thereof according to Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP92/01712

A. CLASSIFICATION OF SUBJECT MATTER Int. Cl^5 C07D401/04, 401/06, 401/14, 413/04, 413/06, 413/14, 417/04, 417/06, 417/14, 471/04, 487/08, 519/00, A61K31/435, 31/47, 31/495, 31/535, 31/54, 31/55
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl^5 C07D401/04, 401/06, 401/14, 413/04, 413/06, 413/14, 417/04, 417/06, 417/14, 471/04, 487/08, 519/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, A, 2-85255 (Toyama Kagaku Kogyo K.K.), March 26, 1990 (26. 03. 90), (Family: none)	1-4
A	JP, A, 62-33176 (Toyama Kagaku Kogyo K.K.), February 13, 1987 (13. 02. 87), (Family: none)	1-4
A	JP, A, 61-251667 (Otsuka Pharmaceutical Co., Ltd.), November 8, 1986 (08. 11. 86), (Family: none)	1-4
A	JP, A, 54-132582 (Bayer A.G.), October 15, 1979 (15. 10. 79), & EP, A, 4279 & US, A, 4284629	1-4
A	US, A, 4617308 (Warner-Lambert Co.), October 14, 1986 (14. 10. 86), (Family: none)	1-4

[x] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
March 9, 1993 (09. 03. 93)	March 30, 1993 (30. 03. 93)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

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